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Special Article

Editor's note—In the routine search for articles of interest to ophthalmologists, Mr. Land's paper in SCIENTIFIC AMERICAN was brought to the attention of Dr. Walls. Almost immediately Dr. Walls felt that any reply to the Land paper should appear in a publication medium whose subscribers had first-hand familiarity with the contents of SCIENTIFIC AMERICAN. Consequently the article below first appeared in PSYCHOLOGICAL BULLETIN, Vol. *57*, January, 1960, and it is reprinted here with the kind permission of the managing editor of the BULLETIN.

"LAND! LAND!"

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On every hand, one hears the cry that a new continent has been discovered in the realm of visual science. Its supposed magnitude is indicated by the titles of some of the articles written about it—"A Bombshell in Color Theory"; "An Astonishing New Theory of Color"; "New Light on the Eye"; and so on.

The discoverer is Edwin H. Land, originator of Polaroid and the one-minute camera, and an undoubted inventive genius in the Edison-Burbank-Kettering tradition. The claims and predictions made by him and for him are not based upon mere novelties of technology, new optical tricks, new types of filters, or new photographic dyes. The underlying discoveries are supposedly so very basic that "a theory of color that has stood for nearly 300 years has suddenly been overthrown . . . the eye does not need red wave lengths of light to see red, does not need orange to see orange (etc.)"; for "scientists since Newton have been completely fooled about the way the eye sees color" so that "every textbook dealing with color will have to be rewritten" (Bello, 1959). We are told that "the recent phenomenon of Edwin Land's essentially 17th-century type of discovery in the field of color vision . . . really shakes every scientist . . . " (Weaver, 1959).

Land's findings are said to be "rightly jarring the imagination of all workers in the field of color reproduction. His public demonstrations made with two slide projectors and usually only one color filter have achieved multicolor effects on the screen which sometimes could not be told from Ektachromes. . . . Land's goal, of course, is a practical, economical one-step method of achieving full-color prints as simply as black-and-white pictures are now made in Polaroid cameras. (Land is developing color material for the one-step camera, but it makes no use of the color-visual principles Land thinks his projection phenomena have uncovered. G. L. W.) The applications, however, could be much more widespread and commercially important. Besides motion pictures and television, which are

closely related to the present projection picture tests, a perfection of a similar system for reflection prints might . . . simplify color ink-on-paper systems" (Cros, 1959). Again, while Land's discoveries "are not yet ready to be applied to color photography" still "there seems little question that this new knowledge will eventually lead to new color-reproduction techniques that will make the present methods look primitive and clumsy. Television especially should benefit from the knowledge that the eye can utilize an entirely different sort of information from what had formerly been thought necessary to produce color" (Bello, 1959).

It will be noted that none of the above quotations is attributed to Land. What he himself has said in print is more conservative. The whole presentation of his material was planned for the *Proceedings of the National Academy of Sciences*. Only Parts I and II have so far appeared (Land, 1959*a*, 1959*b*), but they are perfectly dignified. His *Scientific American* article (Land, 1959*c*) is in a more popular vein, but Land says that wherever it is more excited or seems to claim more than his other two articles, this represents editorial change over which he had no control. He did not even know that the paper of Cros (1959) was in preparation, and he disclaims responsibility for the extravagant article of Bello (1959).

The story goes that early in 1955 Land did begin to consider the possibility of devising a quick process for the Polaroid camera which would yield a print in color in a single while-you-wait operation. To begin to inform himself at firsthand of the problems that would be involved, Land set up, in three projectors, orthodox color-separation transparencies which had been prepared photographically through conventional red, green, and blue gelatine "taking" filters. Screened in registry through similar filters, the images built up additively a full-color reproduction of the original camera scene.

While trying various filters, beam intensities, and so on, Land happened to note that when the blue-filtered projector was turned off there was only a little deterioration of the quality of the reproduction on the screen. In a further "accident," Land removed the filter from the green projector. The intensified white light from it made the picture quite unsatisfactory. But Land's collaboratrix, Meroë Morse (who for a decade has been Land's right arm), noticed that on the screen there were still traces of hues which seemingly should not have been there. At the moment, this was dismissed as a "fatigue" (after-image) effect. Late that night, however, Land returned to the setup and dimmed down the white projector. "Instantly, the scene burst into lifelike color" (Bello, 1959); and since with indefinitely long observation the color array persisted, it was clearly no afterimage phenomenon.

From then on Land's copy, whether still life or animate, was regularly photographed through only two filters. A positive transparency made from a black-and-white negative taken through a red filter (passing only the longer wave lengths) constituted a "long record" and was ordinarily projected through a red filter. A negative simultaneously made through a broad-band green filter provided a black-and-white positive "short record" of the copy. This was rather

a *medium* record, considering what wave lengths and energies would have come through a blue taking filter. The second projector, in which it was placed, usually had no filter over its front lens.

Any object in the original scene was now represented on the screen by a patch of red light coming through a neutral area of a particular density in the long record, and by a congruent patch of white light sent through an identically shaped and sized area of the short record, having (except by chance) a higher or a lower neutral density. The screen "object" was a particular ratio-and-sum of red- and white-light luminances.

An elaborate picture made up of just such objects "should" have presented them all as reds, pinks, whites, and blacks, depending upon the relative and absolute densities of the corresponding patches of the long- and short-record transparency slides: mixtures of red and white lights in the dark-surrounded 3° field of such an instrument as a tricolorimeter could not yield orange, yellow, green, blue, or purple. Land's screen images did show all these hues and, moreover, in "correct hierarchical order"; that is, warm-colored objects of the copy were rendered by about the same warm colors on the screen, and cool-colored objects were represented by cool colors in the picture. Skin looked like skin—in fact more so than in many Ektachrome and Kodachrome pictures.

To Land's mind, here was a great mystery. Where were all the extra colors coming from, beyond those his projection lights could mix to give, when classical color theory could not explain them? By "classical color theory" Land does not mean isolated color-vision theory (Young-Helmholtzian, Heringian, or other), but this together with the relations of hues to wave lengths in the white-light spectrum, Grassmann's laws of color mixture, and particularly the fact that to obtain all hues and white, three additive primary lights are considered to be necessary and sufficient.

If the light coming to the eye from a patch of screen was seen as having a color which a colorimetrist would not expect to see in a mixture of those two lights at those intensities, then classical color theory was inadequate and outmoded. Some entirely new theory had to be developed to account for all the unexpected colors which one obtained by two-light, one-color projection on a screen (and perhaps in no other way).

Quite soon (May, 1955) Land gave the first of his public lectures with demonstrations. The matter then went back into the laboratory, to emerge again in 1957. In that year and the next, Land made presentations to various scientific meetings and university groups, at Washington, Detroit, Rochester, Harvard, and Columbia. The order in which the phenomena came to be shown was as outlined in Land's first publication (1959*a*), where they are described as numbered experiments.

In an orderly way these experiments bring out that: either the red picture or the white picture is monotone or achromatic, but the registry of both makes a tremendous difference since full color then appears; the picture reappears in full color instantly when a flood of room light, which has washed out the screen image, is turned off; enough room illumination can be permitted to enable the

perception of colors apart from the screen, and will not interfere with the colors on the screen; changing the subtense of an "object" at the observer's eye does not change its color; interchanging the long and short records turns red hair and lips greenish or blue-green, showing that the colors are not memory colors nor expectation colors; the hues seen are not much changed by large alterations of beam intensity ratios nor by doubling the contrasts in the short record with superposed duplicates; only red, pinks, and white are seen if the long-record slide is removed from the red-filtered projector—although many intensity ratios are still there; and so on.

Land's oral presentations in eastern cities never came strongly to the awareness of us who stay on the west coast. I first learned of his projection color phenomena when a colleague, who travels much more, pressed Part I (Land, 1959*a*) upon me with the solemn assurance that this was the most important development in color vision in the past 50 years. I read it and forgot it, for I could not see that anything more than "simultaneous color contrast" was involved in Land's securing of hues from red to blue-green when his projection lights were red and green, or red and tungsten "white." Much later, Land's popular article (Land, 1959*c*) was forced upon me, when I was requested to deal with it as a section editor for a condensation journal. By this time Part II (Land, 1959*b*) had appeared, as also the articles in *Fortune*, *Graphic Arts Monthly*, and *Architectural Forum* (Anon., 1959), which were stirring up great excitement and wonderment among all sorts of both scientific and nonscientific people.[1]

In print and in person, Land makes about a dozen serious claims. They cannot be dealt with in either the direct or the reverse order of their "importance," for lesser ones have to be explained before greater ones can be appreciated and *vice versa*. They will be taken up here, therefore, in more or less an order of comprehensibility. First, however, there is to be considered the question of novelty of fact.

Land no longer makes a claim as regards the novelty of the rich visual results of his simple means. In 1955 to 1957 he learned that he was by no means the first to find that two color-separation transparencies are much more than two-thirds as good as three, and that when they are added, one color filter is much more than half as good as two. His latest article (Land, 1959*c*) gives no hint that he knew this (perhaps, one of the editor's doings?), but in his first paper (Land, 1959*a*) a footnote admitted it. As early as 1914, motion picture systems were patented in which alternate frames were taken through a red filter and no filter or through red and green filters, and projected through red and green ones or through a red alternating with none.

[1] It appeared that I should digest these publications and write, if anything, a commentary covering all of them. I wrote to Land to ask whether there were still other articles which I should embrace. The upshot was that I was invited to Cambridge to be shown the phenomena on their home grounds. I might then find myself unchanged in opinion, or disarmed, or even converted. I am grateful for the experience (early in July, 1959), and must say that Land and his devoted associates were most kind, generous with their time and facilities, and patient and fair in argument.

Statements here attributed to Land without literature citation are to be considered in the category of "personal communications," transmitted during my visit to his laboratory.

These systems, and various others which used no filters, but two-dye films which dodged the great difficulties of making three-dye-primary films, gave excellent results so long as the cameraman could dictate the colors of the copy. Pure blues had to be foregone; but there are so few such colors in outdoor nature that they were easily avoided, and the faithfulness of color reproduction was satisfactory. If flesh tones, *i.e.*, skin colors, were good then everything else was good enough. It actually seemed a waste to use a three-color process for a western movie, or even for indoor stories where furniture and costume colors could be selected to avoid those which would come out "wrong."

Even Land's own favorite method for still pictures is not new. In a memorable Optical Society meeting in New York on March 5, 1943, I witnessed demonstrations by Ralph Evans of Eastman Kodak Company, in one of which he projected long and short records taken through the same filters Land now uses, and with red and yellow filters on the two projectors. The hues on the screen, according to notes made at the time, included red, orange, yellow, green, purple, and magenta. Unwittingly Land has even used subject matter similar to one of Evans's own favorites: a redheaded girl wearing a green sweater. The two techniques could hardly be closer, for Land was then using red and orange filters; and even when he is using no filter on one projector and calls the light from it white, this is the strongly yellowish light coming directly from a tungsten filament.

With long and short records of elaborate still-life copy such as assemblages of groceries or bric-a-brac, projected with red and green beams or with red and yellow ("white") ones, it is clearly not the results on the screen which are novel, but Land's explanations of them. Land's full-color results are only the latest of a series of rediscoveries of the same phenomena—first seen, in two-primary projected photographs, at least as early as 1897.

A claim, as good as any to commence with, is that it is just because the subject matter is elaborate, and rendered by good photography, that the many colors appear at all. What is on the screen, Land calls a total image, a complete image, a natural-image situation. The colors seen, except for those of the projection lights and additive mixtures thereof, do not appear when the same lights are mixed in a simple isolated spot. Classical color-vision theories, classical color-mixture laws, do not explain or predict the extra colors. In any place on the screen, the wave lengths and energies just there do not determine the color seen there. If changing the wave lengths changes the colors, it does not do so according to the rules of additive color mixture. The rays of different wave length are not themselves color-making; instead, colors come from the interplay of longer and shorter wave lengths over the entire scene, and it does not much matter what those wave lengths are so long as some are longer and some are shorter. The colors of monochromatic lights and those of colorimeter mixtures are all one big special case, and everyone since Newton has been misled by it as regards how colors arise in "natural" situations.

It is easy to demonstrate that it is Land's color array which is the special case. If his screen is scanned through a slender tube, only spots of red, pink, and white can be found; all other colors vanish. One can take the same tube around the

lighted room or outdoors, and view anything and everything, but hardly any objects will change color hardly at all when seen thus. Land's screen pictures are most *un*natural images.

Now it is perfectly true that the wave lengths and energies at a screen locus do not determine the color seen there. But this does not mean that the color is independent of the light at that locus. It is utterly dependent upon the light in the "object" in relation to the light *around* the object. Even in situations much simpler physically, it is easy enough to see a spot as having any of several hues when spot and surround are constituted of nonselective materials and illuminated by a single monochromatic light. The relative intensities created by relative reflectances are governing here, as shown by Helson (1938) and by Judd (1940), and expressed in Helson's principle of "color conversion" with respect to adaptation levels. In Land's material, one ratio-and-sum of two projection lights represents the object. Other ratios-and-sums surround it—if they were not "other," there would be no object, for there would be no contour.

In his own kind of quantitative analyses, Land has paid much attention to the ratio of the intensity of each kind of light in each object to the maximal intensity of that same light (at some place on the screen). He thus takes careful note of the relative intensity of each light in the object, and of the intensities of the two object-lights relative to each other. He completely neglects the other absolute and relative intensities of the same two lights which are hitting the screen around the object's contours. There are spot-and-surround situations all over Land's screen, and the color of any spot is at the mercy of a *different* spectral composition in its surround unless the luminance of the spot is much higher than that of the surround. No wonder, then, that the color seen in any spot seems to be "independent" of the physics of what is in the spot. To a colorimetrist, Land's most prized phenomena would constitute intolerable artifacts. Colorimetry must be done in a dark or at least a neutral surround. If a sample were matched by mixing in a colored surround of uncontrolled chromaticity, the specification found for the sample would be quite meaningless.

The explanation of his extra colors which Land obviously must controvert, before he can expect our attention to any other explanation, is one in terms of simultaneous color contrast. The expression I myself prefer is "spatial induction (of complementary hue)" for which I shall use induction for short, here. Still a third term for the same phenomenon is "lateral adaptation" which Evans (1943, 1948) points to, along with "general" and "local" adaptation, as being involved in the viewing of any sort of picture in color. For the special case where both spot and surround have the same chromaticity but different intensities, Helson's classical "color conversion" is at work.

There are certain facts about induction which are not generally known, but which are involved in Land's situations (with their action concealed there), and which can be brought out also in the simplest spot-and-surround situations. One usually thinks of induction as it is shown off in an elementary laboratory course, with a square inch of gray paper laid upon a large sheet of colored paper. Here, the phenomenon seems tame indeed. The complementary coloration

induced into the gray is not very convincing, although it becomes more so if a sheet of tissue is laid over all. Tongue in cheek, one tells students that this blurs the contour, and that this facilitates induction across it.

The induction product is far more vivid when it is obtained on a screen with a broad annulus of colored light surrounding a disk of white light from a second projector. At an optimal intensity of the spot, its saturation is maximal. Here again, the effect is promoted if the mutual contour of surround and spot is deliberately destroyed, by moving either slide so that disk and annulus are a bit out of registry.

If now a flood of dim white light is put over the screen with a third projector and gradually increased in intensity, one finds that the colored annulus is quickly washed out—a newcomer entering the room would not dream that any colored light was there; but, the colored spot is as saturated as ever, Kirschmann's laws to the contrary. Specifically, if the annulus is blue the spot is yellow, and when the white wash has completely desaturated the blue the spot still glows like a sun. The durability of the induced color has to be seen to be believed—the white wash cannot wash *it* out. Here is a color which has no visible means of support, and is as unexpected as any color in one of Land's pictures; for, a spectrophotometer will show only white light in the spot and the eye sees only white surrounding it.

When such colors are induced into the very real-looking objects which even a black-and-white transparency puts on a projection screen,[2] their vividness—their apparent saturation, if the term is allowable—is tremendous.

Whatever hue is induced into a spot is inevitably complementary to whatever light, in the surround, is doing the inducing. This is not to say, however, that the surround and spot will necessarily be seen in complementary colors. In Land's pictures, this is rarely the case—which unquestionably influenced him to reject a "contrast" explanation. In the first place, complementariness here is not in the sense of mixture complements—those paired lights which, mixed in a particular intensitive ratio, will comprise a white light—but in the sense of a colored light and the color of its after-image. The mixture complement of a light and its induction or after-image complement are not just the same in hue; there are differences, for known reasons (Helson, 1938; Judd, 1940; Wilson and Brocklebank, 1955). In the second place, a physically chromatic surround may not appear colored at all; or the color seen in a spot may be "mixed" from the direct color of the light actually there and another color induced into it. When a surround is mixed from two beams of light they may both be colored, or, *e.g.*, red and tungsten "white," and in either case the mixture will tend to be seen as white in consequence of general chromatic adaptation. But the red-light content acts as if it were alone in causing lateral adaptation of the retinal area subtending the spot. Truly white light in the spot would now appear white-minus-

[2] An almost forgotten word for a slide projector is *stereopticon* (most likely to be used, nowadays, by mistake for *stereoscope*). It derives from the corporeality which images have when one sees them on a textureless screen and is not forced to see them in a plane, as on a paper print.

red, *i.e.*, blue-green. But if the spot light is itself a little reddish, some of its direct redness can combine with the induced greenness and a little of the blueness to give a basis for neutrality, and the remaining direct redness and induced blueness will make the spot purple. If on the other hand the spot light is yellowish, this direct huedness may kill the blueness of the hybrid induced hue and allow the spot to appear purely green. Furthermore, if a spot is substantially brighter than its surround it can exhibit the hue of either projection light or any additive mixture of the two, while in a spot much dimmer than its surround, induced *blackness* can create maroon, navy blue, olive, brown, and other "synthetic" surface colors. All of these possibilities give way to others, with any manipulation of the ratio and sum of the two kinds of light blended in the surround.

Land's extra colors have a kinship, stronger than he admits, with colored shadows. Produced on a screen with two projectors and a filter or two, shadow colors always come in pairs,[3] which have interesting properties. If both projection lights are colored but not complementary, then quite regardless of what their colors are, the hue of neither shadow is ever the hue of either light since the surround of each shadow is not purely either light. But, the hues of the shadows are invariably complementary to each other. This fact has been known so long that its first discoverer is lost—while its most recent investigator (H. Self, a student of Helson's) has not yet published his work. If the light from one projector is truly white and the other light is hued—say, green—we have a special case. The hue of one shadow will be that same green since the surrounding white-plus-green can induce nothing that will alter it; the hue of the other shadow will be red-purple, induced into the white light in the shadow by the impure green light outside the shadow. Here, side by side, are a "purely physical" (green) shadow and a "physiologic-psychologic" (magenta) one. It is important to note that both shadow colors can be highly and equally saturated while the rest of the screen is acceptably white and necessarily brighter than either shadow—again Kirschmann's laws to the contrary.

With Land-type long- and short-record slides in red and white projectors, one has only to displace one slide to throw the two records out of registry on the screen. One then sees that the "objects" in one slide are represented by a set of colored shadows, not absolute but partial to different extents, but all of the same hue and differing only in saturation and lightness. The other slide is also putting up a set of shadows, of one other (and complementary) hue; and of course the two hues are salmon and aquamarine. Upon pushing the displaced slide back into registry, one can think—for a time—that the additional colors are all created simply by superimposing two complementary sets of colored shadows upon each other.

[3] The most familiar of all colored shadows, the blue ones in a snowscape, may appear to be exceptional. When objects are illuminated both by yellow sunlight and white cloud-light, blue is seen wherever an object blocks the sunlight from the snow. The unseen (adapted-out) yellow surrounding the shadow induces complementary blueness into the white light which, alone, occupies the shadow. No yellow mate to the blue shadow is seen, because the huge white cloud source creates no shadows at all.

When Land claims to be getting full color, this is an exaggeration in two respects. The term implies a faithfulness of reproduction of the copy colors greater than Land does get. It further implies that all possible hues are there, or obtainable, even if some objects have slightly wrong hues. The composition on the screen does exhibit many, many colors (a color being a hue at a given saturation and a particular lightness). If the observer penetrates the glamor of the multiplicity of saturations and lightnesses creating "tints" and "shades," and beautiful surface colors (present by grace of induced blackness), and resolutely hews to the hue circle, he finds that there are gaps in it. Nothing on the screen is really blue without admixture of greenness, and nothing is green without contamination with blueness. Only in casual viewing can one think that some of the palest blue-greens are blue; some of the darkest, green. Land had considerable trouble making a lemon *look* like a lemon with red and white projection—he told me that it took three months of trial and error with taking filters, exposures, and darkroom work.

What can be expected from various ratios-and-sums of red and yellow illuminations inside and outside of object contours? Red, pink, and white of course, with the whites being seen wherever sums are high and the ratio of the two lights is the same as their integrated ratio over the screen (establishing the observer's "white" as his general chromatic adaptation level). Wherever about this same ratio occurs but with a lower or very low sum, there will be a gray or an acceptable black. Upset the ratio but keep the sum fairly high, and there can be oranges and yellows. Then, there will be blue-greens induced by a strong red-light content of surrounds, even when these are adapted out and appear white, or exhibit induction colors themselves. Some of the blue-greens will be greener, passing for green; some bluer, passing for blue. There will be purples, and blackness-containing synthetic surface colors—tans, browns, maroons, navy, drab, etc. What more could one want? What thunderstruck viewer of this marvel would think to ask whether anything in the copy had been sky-blue? Is it just a coincidence that Land's demonstration pictures have all been made indoors, and show objects *he* selected?

Now for Land to say that none of this is described, explained, or predicted by "classical theory" is to be a bit harsh toward centuries of a complex science and a legion of color scientists living and dead. As old as any branch of color science is the knowledge of induced hues—at low saturations, to be sure, prior to electric sources and projectors. They were being exploited in the design of Gobelin tapestries in Thomas Young's lifetime. No one knows how long ago mothers began to teach their daughters what colors to avoid in hats and scarves, so as not to affect their facial complexions adversely. "Accidental colors" were being monographed when people were still arguing over whether three primaries were necessary and sufficient in painting and printing.

It may be that none of Land's technologic predecessors, with two-beam, one-filter color systems, knew just why their systems worked so well. It may be that no one before Evans and Land had the photographic facilities, the filters, and the projectors with which to take such full advantage of induction to produce

such breath-takingly beautiful pictures with such saturations of the unexpected colors. But what needs to be explained is the long list of hues that are there and the short list of those that are not there, and this can be done without making use of any part of Land's explanation. One needs only old information and old language. In fact several languages are available: that of simultaneous contrast, that of spatial induction, Evans's three kinds of chromatic adaptation (1943, 1948), Helson's principle of color conversion (1938, 1955), and so on.

Land explicitly denies that any sort of chromatic adaptation is responsible for his color arrays: "The colors . . . appear immediately, and do not alter appreciably with time, and we do not seek to explain them as effects of adaptation. To the best of our knowledge the gamut of color is much larger than that . . . predicted by any theory concerning chromatic adaptation" (Land, 1959*a*). He formerly demonstrated the immediacy of appearance of the colors by turning on strong room lights which obliterated the screen image, and then switching them off to show that "no visible time lapse" occurs before the full-color effect is seen. A newer device, which he demonstrated to me, is a double shutter with which both beams of his dual projector can be flashed to the screen. Even with only a 0.01-second exposure, the colors are all there. Land considers that since inadequate time is being allowed for any adaptation process, adaptation cannot explain the colors.

Land's trouble here is that in anything he has published, he shows awareness of only the long, slow, intensitive sorts of adaptation which are regulated by the cold-molasses kinetics of photopigment-concentration change. The general and lateral chromatic adaptations which underly contrast phenomena are instant upon presentation of the stimuli (which is why the contrast is *called* simultaneous). They are more akin to the α-adaptation of Schouten and Ornstein (1939) than to the photochemical β-adaptation, and they are readily accomplished by the exercise of inhibitions in purely chromatic pathways, leaving *brightness* vision unaltered (see Walls, 1955). No one to my knowledge has had the hardihood to try to measure the tiny time it takes for induced colors to appear. Since the basis of spatial induction is neural and not photochemical, any time consumed is hardly more than is required for a neuronic message to traverse a couple of synapses. As a matter of fact, simple "persistence of vision" could allow a full manifestation of induction effects even if the presentation time of the stimuli were cut below the period consumed in the induction itself.

By rejecting adaptation, Land brings upon himself just as much trouble in explaining whites and grays, as hued areas. The less stray light there is, escaping from projectors etc., the more surely any colored light or some ratio of any two lights, mixed on the screen, will appear white. It is a familiar experience that even in the ruby illumination of a photographic darkroom, a piece of white paper is subjectively white. In Land's projected compositions there need be no broad white backgrounds, and there need be no broad stray-illuminated border formed by empty screen. Whatever two lights he is projecting with, the observer's "white" will be some intensitive ratio of the two, whether one light is colorimetrically white, or even if both are colored. In any case the average ratio over the

screen will be what the observer adapts to, and he will see white or gray in any discrete area that happens to contain that ratio. The more heterogeneous the copy may have been chromatically, the more closely the observer's white will approach the ratio coming out of the projectors if the slides are removed from them and the intensity controls (already adjusted for best verisimilitude) are left untouched.

A conviction of Land's which is pregnant with several kinds of significance is that the correct hierarchical order of the colors in his pictures, the similarity of the color of each object to that of its model in the original copy, defies explanation under classical theory or in terms of any sort of chromatic-adaptation phenomena. In effect he says that when he began to use his unorthodox primaries he was not expecting close verisimilitude, and has never strained to attain it, but it is there anyway. It is the fact that he obtains a full series of hues "from red to blue" when using only red and yellow, or yellow and green, etc., lights, that must seem the most magical aspect of his results, to those who obtain their scientific information from popular magazines. This degree of verisimilitude secured so cheaply, by such simple means, is what piques the cupidity of those who now contemplate lower costs and higher profits in color photography, color television, and color printing, all as a result of Land's research. And, it was this verisimilitude that originally enticed Land far out on his private theoretical limb. Seeing no basis for it in the stimulus situation, Land attributed the fullness of the full-color gamut to a hitherto unsuspected property of the eye itself. His own further tests of his hypothesis that "the eye can build colored worlds of its own" made with apparatus other than simple lantern-slide projectors, have served only to entrench it in his mind.

The fact that in Land's potpourri pictures the right colors end up, for the most part, in the right objects is only made to seem the more remarkable when one considers that all the hues he ever gets may also be obtained on a screen when the slides projected have stemmed from material that never was colored. One may make two montages of pieces of neutral gelatine filters cemented to glass plates, identical excepting that each piece in one montage is replaced in the other by a congruent piece of a different density. Projected through the same filter(s) Land might use, these will yield the same set of hues on the screen. Just as complete "full color" may even be obtained with photographs, when these are of such character that there is no reason to expect any object to appear in any particular color. This is the case with "long" and "short" records photographed through a dead rat with two different wave length bands of x-rays (and, of course, no color filters), then projected in registry through color filters which "translate" the radiopacity pattern of the subject matter into a color pattern easier to study (see Mackay and Collins, 1957).

If one could not even speak of "verisimilitude" in colored x-ray translations of heads and legs or in colorized neutral montages, how is it that the hues are not random in Land's pictures also? What makes them click into place in the correct objects, unless Land is right in thinking that the eye itself puts them there because it is viewing a "natural image"? Sadly for Land's hypotheses, the veri-

similitude in his pictures is just about as inevitable as it is in Kodachrome. At the same time, paradoxically, it is due to a coincidence.

When Land assembles some objects with hues ranging from red to blue and photographs them through red and green filters, then projects with red and yellowish lights, the long record of a red object is of low density and lets through intense red light, while the short record is dense and lets through little of the other light. Naturally the red object is rendered red. A really green or blue object is represented in the long record by a dense area and in the short record by a pale one. The shorter-waved (or the "white") light predominates in the screen locus of the object. This light however must of necessity appear blue-green or green-blue. This is not at all because the original object had such a color, but because the stronger red illumination around the object-area of the screen induces its complement, and this happens to be an ambiguous hue which satisfies the observer as a reproduction of either a green object or a blue one as the case may be.

It is a beautiful coincidence, at work for Land, that the complement of his red projection light is a blue-green, so close to blue and so very far from red in the spectral series of hues. With selected copy the result is almost full color, and the hasty cannot be blamed for calling it full color. Only pure blue lies beyond the series one does get, for violet is really a purple, the purples are extraspectral anyway, and moreover Land's method does afford some purples! The reason why pure blue is not obtainable is not that blue wave lengths coming from blue copy pigments are stopped by the green taking filter used to make the short record; it is that the long-wave projection light employed has a hybrid hue, not a good blue, as its complement. The projection lights, not the copy colors nor the taking filters, are the real determiners of the set of hues the screen can show. Land, however, thinks of them as the least important elements in the process, as we shall see.

If anyone should fail to grasp the fact that the "nearly full" color of Land's pictures and their fair verisimilitude (excellent for long-wave colors; poorer and poorer—but never *too* bad—for shorter-wave ones) are the results of a beautiful and beautifying coincidence, then I would ask: Suppose the physiology of color vision were such that the complement of red was, say, yellow? How good then would be the verisimilitude?

Land's idea that hue is, or can be, independent of wave length, and his idea that the obtaining of rich coloration from two "primaries" demands a completely new explanation, led him to conclude that "the eye can build colored worlds of its own out of informative materials that have always been supposed to be inherently drab and colorless." When the retina is receiving only two kinds of light which are not very different from each other "the eye" (*i.e.*, the visual system) is apparently able to reassign hue-sensations, which "belong" to the ends of the whole spectrum, to just those two lights, and the intervening hues to mixtures of the two lights.

From a biological point of view, this is by far the most important of Land's claims. It seemingly has profound implications for the course of evolution of human color vision and for its physiology—it seems to demand a complete abandonment of such old-fashioned conceptions as a set of three or four receptor-

types each arousing immutably a unique elementary hue-quality irrespective of the wave length(s) of radiation its unique photochemical contents are absorbing.

In order to determine how close together two projection lights illuminating long and short records could be, *i.e.*, how little of the Newtonian spectrum they could embrace and still give his full color, Land first contemplated using interference filters, with much narrower pass bands than gelatine ones have. Too much intensity would be sacrificed for spectral closeness; so, Land had a high-intensity dual monochromator designed and built. With this he could transilluminate either record with any wave length, seeing the two images in registry by means of a 45° half-silvered mirror.

Land now found that with a wide variety of pairs of monochromatic lights, he could secure full color. It has to be remembered that Land uses the word "color" as if it meant hue. With wave lengths too close together the colors were very unsaturated, and when the lights came from certain regions of the spectrum the gamut of hue itself was much restricted. Land has claimed to get a good result, however, even when the two wave lengths were 579 mμ and 599 mμ. The color illustration prepared by *Scientific American* (for Land, 1959c) which purports to show what then appears on the mirror is very hard to believe.

One phenomenon appeared with the dual monochromator which apparently still puzzles Land, although he has promised a discussion of it. This is what he calls "short-wave reversal." When both of the transilluminating wave lengths are short ones, the very few hues he then gets are in the reverse of a correct order; that is, the coolest-colored copy-objects come out in the least cool hues. This corrects itself if he interchanges the records or the wave lengths so that a violet wave length illuminates the long record and a blue one the short. To my mind the reason for this is that violet has redness in it and blue does not, so that a violet wave length acts like a longer one when it is paired with a blue.

The work with the dual monochromator appeared to support the theory that when only the extremes of a short segment of the whole 300-mμ Newtonian spectrum are available to the retina, the eye exhibits "amazing versatility" and "can respond with a full range of sensation" (*i.e.*, of hues), by reassigning all the hues that belong to a 300-mμ stretch to the wave lengths within a stretch of only 20 mμ or 30 mμ. Somewhere within such a short range there is a point which, Land believes, the eye establishes as a "fulcrum." Wave lengths longer than this, no matter what their absolute values are, are seen with hues which we think of as belonging to the longwave end of the full spectrum, while wave lengths shorter than the balance point are responded to as if they were really short (blue-green, blue) even if they lie in midspectrum.

Out of this reassignment theory arose a corollary hypothesis which Land has quite explicitly outlined (1959c): Suppose the pigments of things around us had very narrow reflection-bands of wave lengths, so that a number of such pigments could be crowded into a short piece of the present visible spectrum, say 30 mμ or 40 mμ long. Suppose also that something should happen to the present solar spectrum reaching the earth's surface—one might imagine light-absorbing ma-

terials getting into the atmosphere—so that only that same 30 to 40 mμ "spectrum" was available to the retina. The colors of the things around us, Land believes, would be just the ones we see now. The reassignment phenomenon prepares us to be transported into any one of many "color worlds."

The basic idea of a "fulcrum" is not wholly wrong, provided one takes the position that it really expresses Land's own unconscious rediscovery of general chromatic adaptation. If one projects pictures or shadows with yellow and blue-green wave lengths and gets red and blue on the screen, the red sensation is not being "assigned to" the yellow wave length but is induced by the blue-green one, and the blue is not assigned to the blue-green but is induced by the yellow. One wave length would indeed appear here to be a fulcrum—the dominant wave length of that Y-BG mixture which, through general chromatic adaptation, had become the observer's "white." But the eye does not select this wave length out of what is coming into it, and use it in a particular way, for it need not be present in either stimulus.

With the original method using slide projectors, Land had found that "white" (unfiltered tungsten-) light could serve as a "primary" just as well as the purest of color-filtered lights. The dual monochromator contained a pair of hinged white surfaces, each of which could be swung into position to occlude one of the diffraction gratings and reflect the undispersed tungsten-lamp light through one slide to the 45° mirror and the observer's eye. This arrangement enabled Land to confirm that when shortwave monochromatic light came through the short record and white light through the long, the picture contained reds as though the white light were a long wave length. When white light was sent through the short record and long-wave monochromatic light through the long one, the picture exhibited blues as if the white light were a short wave length.

This led Land to pose the question, "what is the wave length which is equivalent to white, the wave length than which white is neither longer nor shorter?" Such wave length would be that which the eye employs as "the fulcrum in the ordinary, sunlit world," with respect to which the visual system assigns a redness sensory quality to the longest other wave length available and a blueness sensation to the shortest other wave length coming into the eye. With white light going through one record and monochromatic light through the other, the observer would find the fulcrum wave length as that one which made the picture go neutral or monotone all over.

All but two out of Land's many subjects, told to watch a red "object" and rotate the wave length control until it started to turn green, found the "fulcrum" at λ588 ± 2 mμ. Considering that the "white" light here was again yellow tungsten-filament radiation, it is immediately evident to anyone with a smattering of colorimetry that this was no experiment, but a simple observation—a determination of the dominant wave length of the tungsten emission, *i.e.*, that wave length which would have the same hue to the observer as the tungsten light itself. No mixture in a surround, of any two lights having the same hue, however different in purity, could possibly induce any hue into any mixture of the same two lights in the surrounded spot. The two odd observers (one male, one female)

who found a rather different "sunlight fulcrum" wave length must have had unusual lens pigmentations, unusual luminosity curves, or some such things. Both had normal color vision, for I checked them myself with my own Nagel anomaloscope, which I had with me in Cambridge.

The dual monochromator work made it appear that white light could give a sensation of red, blue, or any color depending upon what monochromatic light it was paired with; and, it seemed to show that almost any wave length could arouse a sensation of almost any hue, depending upon what other wave length, far enough away, *it* was paired with (Land, 1959*b*, 7959*c*). To demonstrate these things convincingly to a group, with something other than a one-man, eyepiece instrument, Land devised another apparatus in which he took advantage of the fact that one particular wave length of monochromatic light is easily available at very high intensity from an inexpensive source: a standard sodium vapor highway lamp emits λ589 mμ.

In one of his two "sodium viewers" (Land, 1959*b*, 1959*c*), a short-record transparency with the objects enlarged to natural size is transilluminated by tungsten lamps and viewed through a 45° half-silvered mirror, and the long record (reversed right for left) is transilluminated by a sodium luminaire and seen in the mirror, so that the two color-separation pictures are optically coplanar and congruent. The observer looks into this viewer through a hand-held green filter which transmits λ589 mμ, and then has the effect of a dual-projector-and-screen setup with green-filtered and 589 mμ projection lights. In the other viewer the λ589 mμ comes through the short record and the long record is tungsten-illuminated through a red filter. In the first viewer, λ589 mμ is longer than the dominant wave length of the green short-record filter; in the second viewer, λ589 mμ is shorter than the dominant wave length of the red long-record filter.

The picture of groceries which Land presents with the green filter contains some objects partly or wholly red, in particular a vivid red can of pepper. Land asserts that here it is the λ589 mμ coming from the pepper-can area which is arousing the red sensation. In the other viewer, where λ589 mμ is the shorter-wave stimulus, some objects appear in cool hues, notably a blue-green book binding. Here, Land claims that λ589 mμ is arousing *that* sensation. So, if one and the same wave length can "be" red at one time and green or blue at another, the thesis that the eye reassigns various hues to wave lengths to suit itself is abundantly proved.

The sodium viewer experiment proves no such thing. Consider what is making the famous pepper-can red through the green filter. The can is dense in the short record, pale in the long, hence is represented by bright 589-light and dim green light. Since the surround of the can in the copy was *not* red, it is represented by relatively intense green light and feeble 589-light. The green induces a strongly red purple into the can area. Here the blueness element of the purple encounters the direct yellowness of the sodium light and they kill each other off (after the fashion of complementation), leaving the redness to be seen alone in the can. The key to what is really going on is given by the individual variation that transpired when I myself viewed this demonstration in Cambridge. For me, the pepper-can was a slightly bluish red, a magenta. I did not develop enough yellow-

ness to kill all the blueness that was there for me. Another person present called the can purely red. A third and fourth called it orangeish-red—for them, there was more than enough yellowness, or else less blueness in the hybrid complement induced by the green light. What was varying here, of course, was the shape of one's personal curve of "the intrinsic saturation of the spectrum."

There are other ways to describe the genesis of the red pepper-can; but they are all in old languages, requiring no supposition that "the eye is revealed to be an instrument of unsuspected and awe-inspiring subtlety." So far as I am concerned, the red of the pepper-can is being seen where the λ589 mμ *is*, but it is the adapted-out green in the can's surround that is putting the red there. The same surround would induce redness into any other light substituted for the λ589 mμ, just so its direct color was low enough in saturation. In the red-filtered sodium viewer, it is just as clear that any green-blue or blue-green seen in any object is only the expected induction product of the more intense red light in the surround, which readily overwhelms the direct yellowness of the λ589 mμ (yellow being the least saturated locus in the spectrum).

Land, believing strongly as he does in his theory that color vision works by assignment of hues to available wave lengths simply according as they are longer or shorter, has been led to a philosophy about the evolution of human color vision which Bello (1959) quotes directly from one of Land's 1957 public lectures: "Would it be possible, in a system which had only a pair of receptors balancing off against each other somehow, for the animal to have a sense of a full range of hues running from red, orange, yellow, green, down into blue? That animal could see the leopard in the leaves in a way that his competitors couldn't. He would survive the leopard . . . and go on to build the world we live in." Elsewhere (1959*c*) Land has said:

". . . we have not been describing a two-color theory of vision. . . . It is true, however, that our experiments deal with two packages of information . . . the eye can do almost everything it needs to do with these two packages . . . there is not a very big gap in the sensation scale to be filled . . . the visual process will remain an amazing one from the evolutionary point of view. Why has a system that can work so well with two packages of information evolved to work better with three? . . . we feel that the big jump is obviously from one to two (p. 99)."

Translated into language which most color-vision researchers would use, this means that Land views the course of evolution of primate color vision thus: Originally, a single receptor-type afforded only monotone or achromatic imagery. Upon the differentiation of this into two types the system became able to give to consciousness the hues from red to bluish blue-green, some purples, neutrals, surface colors (containing blackness), all by assigning the extremes of the hue series to the extremes of any available stimulatory wave length band. Essentially the only hue missing was purest blue. It is hard to see why the organism went on to add 50 per cent more mechanism (a third receptor-type and all accessory neurons) just to secure this one more hue for the sensory gamut; but this did happen.

The catch here is a double one. In the first place, at a point in evolution prior

to the invention of a blueness receptor in the retina, the higher levels of the system would not have embodied mechanism for putting any blueness into any sensation, whether by induction or otherwise. Man's present three-component system affords redness, greenness, and yellowness synthesized from their bases, together with blueness, and all of these hue qualities either singly, or in blends of two, can get into sensations—courtesy of induction—when only red and yellow (say) lights are impinging upon the retina. But these lights, or any two others, or any one light, activate all three components of the system. In an earlier, two-component stage of the system, no more hue qualities than red, possibly (but probably not) yellow, and green could have been enjoyed.

Land errs in saying (1959*c*) that the central idea of the three-component theory of color vision is that "the eye responds to three different kinds of vibration, and all color sensation is the result of stimulating the three responses in varying degrees of strength." He attributes this to Maxwell and Helmholtz, who instead believed that each receptor-type responds to some extent to every wave length in the visible spectrum. One has to go back to Thomas Young for the short-lived idea that each receptor is activated primarily by one bit of the spectrum (one "kind of vibration") and responds at all to neighboring frequencies only in "forced vibration." Land seems to think that if he uses two projection lights, the hue of neither of which has any blueness about it, he is stimulating only two components and the third might as well never have evolved—all the hues now seen by an observer *with* a three-component system being those which would have been seen by the remote ancestor who did not yet have any blueness component at all.

In the second place, we have people with two-component systems all around us—the dichromatic color-blinds. They comprise three or four very different types, but we know that not one of them sees more than *two* hues in the entire white-light spectrum. The color-normal experiences perhaps 40 hues.[4] Dichromatic vision is "a big jump" above monochromatic, but it does not afford 40 − (pure blue) = 39 hues. Even though the color-normal sees many more colors in a Landian two-projector picture than the simple stimuli seem to be worth, this would not be true for a dichromate. For him, any wave length to one side of a neutral point can induce only the same one-and-only other hue that he gets directly from any wave length on the other side of the neutral point. With long and short records projected through red and green filters, a normal may see on the screen reds, oranges, yellows, chartreuse, greens, blue-greens, purples, and neutrals. A tritanope standing alongside would not see more than one kind of red and one kind of green, each at various saturations down to zero (neutral).

While most of Land's color research thus has to be called much ado about nothing new, it would be a mistake to say that it is all just a flash in the pan-

[4] This has to be a guess. It is commonly taught that there are about 120 discriminable hues in an equal-brightness spectrum and 20 to 30 extraspectral purples. There may be 120 values of $\Delta\lambda$, but each is a complex of hue and saturation. The curve of "$\Delta\lambda$ *vs.* λ" has never been determined in an *equal-saturation* spectrum. It is not a "hue discrimination curve," but a wave length discrimination curve.

chromatic! Land's "new coordinate system" and the relationships he can extract from it are probably salvageable (although Judd's 1940 formulations might be as fruitful in the projected-color situations, or more so). It may well be that in the hands of Land and others the coordinate system will enable a quantification and accurate prediction of induction products which never could have been had, or had easily, without it. This may be only my own wishful thinking, stimulated by a considerable sympathy for Land. I myself am not qualified to quantify anything more complex than my bank balance.

Land's coordinates are cartesian, but nothing else about them is conventional. The ordinate axis is a logarithmic scale of "percentage available long wave length stimulus" and the abscissa axis bears a log scale of percentage available short wave length stimulus. With long and short records in projectors or in the dual monochromator, and any two projection lights, any point on the screen finds a place also as a point on a graph with these coordinates. When the beams have been regulated for best color array, the short-record illuminant is cut off and the maximal intensity of the long record image is found and measured, with this luminance then taken as 100 per cent. The relative intensity at any other locus gives an ordinate value for that locus. Abscissa values are found in the isolated short-record image, as percentages of the highest intensity anywhere in the image. One point on the graph may, of course, represent any number of image points where the same absolute luminances of the two kinds of light happen to occur. These various physically identical image loci should not exhibit the same color unless they all have identical surrounds; but Land appears to claim that they do, since on a sample graph, given in all three of his papers, he labels single points with single color names.

Each point on the graph represents a relative intensity relative to another relative intensity, and is supposed to describe and predict a unique color on the screen. This has helped to make it appear to Land that "the eye turns brightness ratios into colors" (Bello, 1959), although, as pointed out above, he considers only ratios in spots and neglects ratios in surrounds and ratios of spot ratios to surround ratios. Land emphasizes that his coordinates are dimensionless, scaled in naked numbers. Actually, since a new graph has to be made for every pair of color-separation positives and for every pair of lights used for every picture, the coordinates could be calibrated directly in log luminance. It is hard for me to see why they are not, for the percentage scales do not generalize or universalize the graph. The predictive values of any one graph are confined within itself, for that graph can tell nothing about what colors will be seen, or where, in another picture with other lights or even with the same lights.

Land soon noticed that all of the whites, grays, and blacks on the screen plotted along a 45° line in his coordinate system. This is logical, for on the 45° line the arithmetic ratio of the intensity of one light to the intensity of the other is a constant. If a screen point with this ratio and some sum appears neutral, any other point with the same ratio and another sum should appear neutral; and, this ratio is the one which ordinarily would exist all over the screen if the slides should be removed from the apparatus. Land calls the 45° line the "neutral

line" or the "gray line"; it could as well be called the "general chromatic-adaptation line" or the "adaptation level." Since warm colors necessarily plot above the 45° line and cool colors below it, one readily sees whence came Land's idea that the Newtonian spectrum is a physical artifact of prisms and gratings and that the real visual scale of sensation runs from warm hues through neutrality to cool hues.

One has to read with caution Land's description of the properties of straight lines other than the 45° one, on a graph in his coordinates. He calls them "achromatic tracks" and includes among these the ordinate and abscissa axes themselves. Just as one has to know that when Land says color he means hue, so also one has to know that when he says achromatic he means achromatic-or-monotone—he makes no distinction between a set of screen points which all have the same hue, and a set which all have no hue. Anything short of full color, he is likely to dismiss as no color.

Among these "achromatic" straight-line loci are the rotated or displaced (but still straight) gray line which results from doubling the contrast in one image (by using two layers of short-record transparency), and a line at right angles to the normal gray line. Such a line is the locus of all that one can get on the screen by projecting any negative in registry with a positive made from it. This is not necessarily an "achromatic" (monotone) situation, for the line may cross the gray line and continue into the "cool" area: although one sees only reds, pinks, and whites if a dark negative goes through a red filter and the bright positive through none, one may get reds, neutrals, and blue-greens if the positive is red-filtered and the negative is tungsten-illuminated.

This negative-positive combination serves to exemplify some situations which puzzle even Land, and baffle me completely. On the screen, each object may be represented by one of the very same ratios of intensity of the projection lights that would be on the screen if long- and short-record positives were in the projectors. But, the negative-positive screen picture is monotone or at best bicolor. This is not because the negative is always so dense that all surrounds contain essentially only the positive projector's kind of light—Land convinced me of that by projecting a negative and positive of his "standard objects slide" (illustrated in Land, 1959*a*) where, since the background in the copy was a mid gray, it is about equally translucent in both positive and negative.

Another mysteriously "achromatic" situation is obtained by projecting three identical positives made from any negative (color separation, or not) with two superimposed in one projector, the third alone in the other projector, and a color filter over each lens. The screen loci again receive an enormous number of ratios of the two kinds of projection light. Perhaps Land's "doubled gamma" transparencies have always been too dense over most of their area, for I have learned of two other people, who have work in progress on this matter, who do get the various hues in the "three identical images" situation.

Thus, there are situations in which brightness ratios as such do not get "turned into colors" by our clever eyes. I don't know why one doesn't always get new colors when one mixture of two colored lights is surrounded by another mixture

of the same lights. In all of the situations Land finds to be "achromatic" there is a common feature, in that there are regular progressions of ratios. This in itself is enough to lead him to expect no gaudy results. He justifies his use of elaborately-composed photographs to begin with (instead of "scientific" spots-and-surrounds and montages of "scientific" Munsell papers) by insisting that randomness of the projection light intensity ratios and of their topographic distribution over the screen is essential for the varicolored effect. Such randomized configurations are, he says, natural; and it is in natural images that he has found the truth about color vision.

One of the tests with which he "proves" the necessity of randomness, and the color-killing effect of regularizing in any way the intensity-ratio array on the screen, is the experiment with neutral step wedges. With two such wedges in place of slides, one oriented horizontally in one projector and one vertically in the other, and with a red filter over one projector, one gets on the screen only a huge square which is red in one corner, white in the opposite corner, and pink in between. Yet, a great number of intensity-ratios of the lights are there (256, to be exact), just as in one of Land's beautiful long-and-short-record pictures.

When I asked for black grids to be put on the wedges, which would themselves be in registry on the screen, and this was done, the screen was no longer monotone but exhibited several hues. Any illuminated square now had, nearest to it, other squares in which the ratios were different enough to be capable of inducing something into the first square. To my own satisfaction this showed that it is not randomness *per se* but *discreteness* that is essential, for the ratios in the squares were still in a regular topographic array. The virtue of Land's photographs of hodgepodges is that the easy way to get discreteness—local changes of ratio large enough to create contours—is by permitting randomness, which is rife in just such photographs.

And with this, I can strike my closing note, which is that I am quite content with being able to explain why Land gets what he does get, using only old knowledge and old language and making no use whatever of Land's fantastic new hypotheses and new concepts. I leave it for others to explain why he doesn't get what he doesn't get, *i.e.*, why the "unexpected" colors are lacking where he has come to expect them, as in his various "achromatic" situations. In each of these, I am sure, some simple principle—which just happens to escape nonmathematical *me*—will explain the nonappearance of "full color."

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Refresher Lecture

THE A-V SYNDROME

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Recently it has been found valuable to add two cardinal directions of gaze to the previous six cardinal directions of gaze in the measurements of strabismus patients.

It has been noted that some esotropic patients decrease their esotropia in straight upward gaze and increase their esotropia in straight downward gaze; this has been referred to as esotropia with the V syndrome. An example of this would occur with an esotropia of 10° in straight upward gaze, 20° in gaze straight to the front and 30° in straight downward gaze.

Some esotropic patients manifest greater esotropia in straight upward gaze and less esotropia in straight downward gaze. This has been termed esotropia with the A syndrome. An example of this would occur with an esotropia of 30° in straight upward gaze, 20° in gaze straight to the front and 10° in straight downward gaze.

The same phenomena have been observed in exotropia, *i.e.*, upward gaze increasing the exotropia and downward gaze decreasing the exotropia, thereby producing the V syndrome with exotropia. An example of this would be an exotropia of 30° in straight upward gaze, 20° in gaze straight to the front and 10° in straight downward gaze.

Some exotropic patients manifest less deviation in looking upward and greater deviation in looking downward. This situation produces the A syndrome with exotropia. An example of this would be an exotropia of 10° in straight upward gaze, 20° in gaze straight to the front and 30° in straight downward gaze.

Although the terms A and V are relatively new in our terminology, Krewson[1] has pointed out that these conditions have been recognized by Duane, Bielschowsky, Chevass, White, and others by other terms.

In order to recognize the A and V syndrome it is necessary to examine patients in straight upward gaze and in straight downward gaze. These are the 2 additional cardinal directions of gaze suggested earlier in this paper.

The occurrence of these A and V syndromes is not infrequent. They are seen almost daily now that we are looking for them and examining patients looking straight upward and straight downward. Costenbader[2] has reported finding

significant difference in horizontal strabismus in looking straight up and straight down in one-third of his patients. This may be of great significance in determining the cause for some of our failures in horizontal strabismus surgery in the absence of any demonstrable vertical muscle palsies. One of the most interesting aspects of these syndromes is that usually no vertical element can be uncovered, or the hypertropia is very small and of little consequence.

What are the possible causes for the A and V syndrome? Most of the extraocular muscles have been proposed as etiologic factors by different authors. Urist[3, 6] has for some years now considered the lateral rectus muscle to be of importance in upward gaze and the medial rectus muscle to be of importance in downward gaze. Urist believes that in the V syndrome with apparent overaction of the inferior oblique muscles the primary dysfunction is an overaction of the medial rectus muscles in esotropia and overacting lateral rectus muscles in exotropia. Urist feels that in the A syndrome with apparent underaction of the inferior oblique muscles or overaction of the superior oblique muscles the primary dysfunction in esotropia is underaction of the lateral rectus muscles and in exotropia underaction of the medial rectus muscles.

Breinin[7] has demonstrated electromyographically the increased firing in the lateral rectus muscle in upward gaze and inhibition of the medial rectus in exotropia with the V syndrome. He has also shown the reverse to be true in downward gaze, *i.e.*, increased firing in the medial rectus muscle and inhibition of the lateral rectus muscle producing an exotropia with the V syndrome. In exotropia with the A syndrome, Breinin[7] has demonstrated decreased firing in the lateral rectus muscle and increased firing in the medial rectus muscle in upward gaze. He has demonstrated decreased firing in the medial rectus muscle and increased firing in the lateral rectus muscle in downward gaze in the A syndrome.

Similar changes are noted in esotropia A and V syndromes.

This evidence of course points to the medial rectus muscles and the lateral rectus muscles as etiologic factors—the medial rectus muscles deviating the eyes inward in downward gaze and the lateral rectus muscles deviating the eyes outward in upward gaze. Therefore, the effect of the vertical muscles would be due to their advantageous or disadvantageous mechanical position and not to an innervational defect on their part.

The obliques both inferior and superior are abductors, whereas the vertical rectus muscles, both inferior and superior are adductors.

Jampolsky,[8] in opposition to Urist's and Breinin's findings, believes that exotropia with the A syndrome is due primarily to an overaction of the superior obliques, *i.e.*, as the eyes look straight downward, the abducting superior obliques force the eyes out. He cites as evidence for this: (1) the production of the exotropia A syndrome by bilateral inferior oblique myomectomies or myotomies; and (2) amelioration of this syndrome with bilateral superior oblique tenotomies. Jampolsky[8] has demonstrated the fact that bilateral superior oblique tenotomies may diminish the esotropia in downward gaze by 45 prism diopters, with very little effect on the horizontal deviation in upward gaze or gaze straight to the front. He also reminds one of the fact that there may be marked alteration in the

horizontal deviation produced by bilateral anomalies of the superior obliques, *i.e.*, as much as 60 to 80 prism diopters of esotropia in downward gaze with little effect on the horizontal deviation in upward gaze. This would be due to abduction insufficiency—the superior obliques being abductors. Thus we see that Jampolsky's explanation for the A and V syndrome in downward gaze is due to overaction or underaction respectively of the abducting superior oblique muscles. He implies, but does not state emphatically, the same explanation for the A and V syndrome in upward gaze as being due to underaction or overaction respectively of the abducting inferior oblique muscles.

Brown[9] has proposed the cause as being due to overaction of the superior and inferior rectus muscles, much in the same manner as Jampolsky suggested the primary pathology to be in obliques. That is, exotropia with the V syndrome would be due to underaction of the adducting superior rectus muscles; exotropia A would be due to underaction of the adducting inferior rectus muscles; esotropia with the V syndrome would be due to underacting superior rectus muscles; esotropia A would be due to underacting inferior rectus muscles.

Regardless of which one or combination of the above etiologic factors may be correct, one must remember that these syndromes show no true paresis or paralysis of the vertically acting muscles. One may have an A or V syndrome with paresis or paralysis of a vertically acting muscle or muscles, but we will not be concerned with these cases in this presentation.

TREATMENT

The treatment of the A and V syndromes at the present time seems to center around correcting the etiologic factor, or factors, thought to be active in the production of the A and V syndrome in each individual case.

When faced with a case of exotropia with an A syndrome and overaction of both superior oblique muscles, bilateral tenotomies of the superior oblique muscles would seem to be a reasonable approach. One must, however, adhere closely to Jampolsky's strict criteria for this; *i.e.*, the patient should exhibit at least 45 diopters more exodeviation in straight downward gaze than in straight upward gaze. It is apparent in these patients that fusion is to be lost due to the increased exodeviation. One must also remain aware of the potential dangers of weakening depressor muscles, the position in which the eyes spend most of their waking hours.

In exotropia with the V syndrome bilateral myotomies of the inferior oblique muscles may be done. Here one may only expect to correct approximately 15 diopters of deviation, however. Tenotomies of the superior oblique muscles yield a much greater horizontal correction (45 diopters as opposed to 15 diopters) than do myotomies of the inferior oblique muscles. Appropriate horizontal muscle surgery may be combined with the above oblique surgery. This must be determined by the amount of exodeviation present in the primary position of gaze. In exotropia with the A syndrome one might find it necessary to combine a strengthening procedure of one or both medial rectus muscles with the superior oblique muscle tenotomies. With the V syndrome recession of the lateral rectus

muscles might be found necessary. This would tend to aim treatment at etiologies supported by Urist, Breinin and Jampolsky. This may sound a bit "all encompassing" but perhaps both the vertical acting muscles and the horizontal-acting muscles do play a part in the production of these interesting syndromes.

In esotropia with the V syndrome, Costenbader,[2] recommends recession or myotomies of the inferior oblique muscles—either alone or with resection of the lateral rectus muscle or muscles—when the esotropia in the primary position justifies it. Tucking of the superior obliques with or without recession of one or both medial rectus muscles would seem to this writer a more logical approach.

Krewson,[1] has pointed out the necessity in esotropia with the V syndrome of a trial with bifocals.

In esotropia with the A syndrome Costenbader,[2] reports his best results with resection and advancement of the inferior oblique muscles, along with resection of the lateral rectus muscle or muscles. He also reports good results with tenotomies of the superior obliques.

The treatment suggested to date has been primarily surgical. More time and experience will be required to adequately evaluate the long range results of the suggested surgical therapy.

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Clinical Practice

THERAPEUTICS

TREATMENT OF MYASTHENIA GRAVIS WITH PROLONGED-ACTION MESTINON

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With the recent introduction of Mestinon (pyridostigmine bromide) and Mytelase (ambenonium chloride), considerable progress has been made in alleviating the weakness of the patient with myasthenia gravis. Mestinon has proved to be more effective than neostigmine because of its longer action and fewer side reactions. The major purpose of the present study was to evaluate 90 mg. and 180 mg. Mestinon bromide Timespan tablets. They were given to 20 patients previously adjusted on varying other medical regimens. The tablets containing 180 mg. represent 3 times the dose of the ordinary 60-mg. Mestinon tablet.

As with all myasthenic drugs, optimum doses of Mestinon bromide Timespan varied widely, ranging from 180 mg. per day to 1080 mg. daily in this series. In general, patients needed slightly larger doses of Mestinon bromide Timespan to give equivalent strength to regular Mestinon. This suggests some slight impairment of absorption of the total dose or suboptimal levels. However, the patients, in general, had no significant difficulty adjusting to this slight increase in dose.

Prolonged-action Mestinon is most valuable in night-time treatment. The drug eliminates the need for sleep interruption to take further medication and leads to better strength in the morning. Some patients feel that Mestinon bromide Timespan is the best available medication for their myasthenic symptoms during the day, but many do not think that the preparation is significantly better in this regard than regular Mestinon or Mytelase.

The patient must understand the nature of the tablet and its potential side reactions. In general, muscarinic side reactions are no more prominent than with regular Mestinon. It was noticed that the larger-sized tablet prepared with two cores might cause diarrhea and cramps in the early morning. This was, however, not a significant complaint with proper dosage. The patient begins with a tablet of the medication, noting the time and duration of effect.

The initial preparations were prepared to release multiple doses and consisted of an outer and an inner core; the inner core supposedly liberated the drug at a later hour than the medication in the outer core. However, for the past year, the method of preparation of both 90-mg. and 180-mg. tablets of Mestinon bromide Timespan has been altered so that the active ingredients are distributed throughout the tablet mass more or less uniformly. This method utilizes an absorbent and presumably provides for a more uniform release with no provision for a prompt loading dose as was provided in the outer core of the older tablets. These new tablets have a tendency to take on moisture and become fused together, but this problem was solved by packaging each 100 tablets with a silica gel dehumidifier.

Mestinon bromide Timespan is relatively safe and does not offer significantly increased chances of toxicity over and above the other antimyasthenic agents. However, as with all the effective anticholinesterase compounds, the potential dangers of cholinergic crisis must be remembered. The physician administering this drug should use the same principles of therapy as with the other anticholinesterase drugs.

Comment: It is apparent that attempts are being made to obtain drugs which will allow more satisfactory handling of the patients afflicted with myasthenia gravis. These prolonged action drugs, such as Mestinon, the dimethylcarbonate of 3-hydroxy-1-methylpyridinium bromide, would seem to offer an advantage to many patients. Similarly, the prolonged action tablets of neostigmine bromide can be helpful. Magee and Westerberg called attention to the fact that patients afflicted with ocular myasthenia type of the disease show less significant response to all antimyasthenic drugs than those showing generalized myasthenia. For this reason Leopold and his associates have evaluated the use of locally applied anticholinesterase agents in patients with ocular myasthenia with definite improvement in a majority. Very little has been done with this approach, and it is possible that this may offer more help in the management of the ocular myasthenic patient.

IRVING H. LEOPOLD

RODENT ULCER OF THE CORNEA (MOOREN), TREATED BY SURGICAL DIATHERMY

CASE HISTORY

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Rodent ulcer of the cornea is a rare and serious affection; its etiology is unknown, and its therapy has resulted in many failures. Up to the present not more than 150 cases have been presented in the literature.

The chronic evolution of this ulcer lasts from 2 to 10 months, sometimes even longer, and its localization is superficial. The affection has a progressive intermittent course, in form of crises; quiescent periods alternate with periods of exacerbation, accompanied by violent pain in the eye. In its progressive development, the ulcer can invade the whole cornea, and destroy its surface. The process of cicatrization follows the ulcer and leaves a total superficial ulcer which profoundly alters the patient's vision.

There is an ample therapeutic armamentarium for rodent ulcer, but it is far from satisfactory. Recently β-radiations have been used, 1000 r once a week, in four successive sessions. In 45 cases, 15 cures, 14 improvements, and 16 cases without result were obtained by Ledermann (Brit. J. Ophth., 1957, *41:* 1), that is real success in 30 per cent of the cases. Up to now little use was made of diathermy for rodent ulcer of the cornea.

The author reports on a case of rodent ulcer of the left cornea, where a cure was obtained with treatment by diathermocoagulation within a very short period of time, under optimal conditions. The 52-year-old patient suffered from a rodent ulcer at the lower part of the left cornea, a classical form of this disease; there was no apparent anterior cause. The evolution of the disease was very serious, and it resisted local conservative treatments as well as surgical intervention. The latter consisted in a simple excision of the ulcer followed by a conjunctival autoplasty. The bimicroscopical examination revealed an important vascularization along the invading edge of the ulcer, in full corneal tissue. This vascularization was destroyed through diathermocoagulation which brought about a cure by stopping quickly and permanently the corneal ulcerating process. All other treatments, including antibiotics, had remained without effect on the aggressive evolution of the ulcer.

After the failure of previous treatments, diathermocoagulation was begun September 13. On September 14, the ocular reaction was minimal. The cornea was almost completely cicatrized. Only two isolated points persisted which colored with fluorescin. On September 18, another diathermy achieved complete cicatrization of the ulcer within the 11 following days (September 29). On October 2, the patient left the hospital, completely cured. He was seen again 4 months later; the cure was complete and the visual acuity 2/3.

During diathermy, the electrode was applied to the demarcation line between the ulcer and the clear zone of the cornea, that is to say to the subconjunctival border of the ulcer, exactly in the zone of invasion. The duration of the contact was 1 to 2 seconds; the application was carried out without pressure in order to spare the zone of the cornea affected by the ulcer.

Comment: Ever since Mooren in 1867 first described the progressive ulcer of the cornea known by his name, many forms of therapy have been attempted with little success. We must of course be wary of any one case which does respond to a form of treatment. Nevertheless, it is interesting to note the improvement that occurred in this patient's eye following the use of diathermy to destroy the vascularization which was proceeding along the invading edge of the ulcer.

IRVING H. LEOPOLD

LA PYRÉTHOTHÉRAPIE EN OPHTHALMOLOGIE

RECHERCHE DE CERTAINES CONSTANTES BIOCHIMIQUES DANS LE CHOC PROTÉIQUE

(PYRETOTHERAPY IN OPHTHALMOLOGY)

(RESEARCH ON SOME BIOCHEMICAL CONSTANTS DURING PROTEINIC SHOCK)

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Thermic increase creates in the organism a series of modifications, such as (1) general metabolism, (2) hematocyte reactions, (3) hematoplastic reactions, (4) endocrine reactions, and (5) reactions of the nervous system.

In the authors' experience, fever therapy constitutes one of the adjuvant methods currently used in various affections, combined with local as well as general treatment.

Twelve cases of various ocular affections were studied: eczematous blepharokeratoconjunctivitis, 1 case; trigeminal neuralgia, 1 case; ptosis with probable myasthenia, 1 case; interstitial keratitis, 1 case; cataract, 3 cases; ocular traumatism, decompensated cardiac insufficiency, 1 case; optic atrophy, 1 case; glaucoma, 1 case; and iritis, 2 cases.

The following modifications were observed during proteinic shock:

1. Glycemia increases during the fever period of the proteinic shock, and returns to its initial value when the temperature falls.

2. A diminution of the values of the total proteins can be observed during the thermic rise; then follows a return to the initial values and even an increase compared to the latter.

3. The proteinic formula shows the decrease of albumins in all cases under observation, and a modification of the globulins, for there is an increase of α-II and β-globulins. The variations of the γ-globulins are irregular.

The proteinic formula after the fever shows an increase in γ-globulins. The increase of γ-globulins explains the total protein increase as determined by means of the refractometer. The augmentation of γ-globulins after the fever leads us to think of a mobilization of antibodies; this would explain the satisfactory therapeutic results achieved by means of milk protein therapy.

4. The 17-ketosteroids eliminated by the urine vary diversely, but a fall from the initial value can always be observed after the last milk injection. This might prove insufficiency of the adrenal cortex. But if we compare the results obtained in the elimination of the 17-ketosteroids by the urine with the aspect of the pro-

teinic formula, we arrive at the following conclusions: In our case an increase of proteins and a decrease of elimination of 17-ketosteroids by the urine are observed. This suggests their retention in the tissues, and it is well known that the corticoids intervene in nitrogen metabolism by accelerating the protein anabolism —a fact which in this case is also proved by massive increase of the globulins.

The patients studied in the clinic received milk injections varying in dosage from 10 to 14 cc. Approximately 6 hours after the injection a temperature increase up to 38 to 39° takes place. The following procedure was developed: Three injections were given to each patient in 3-day intervals. The elimination of 17-ketosteroids in the urine was examined 24 hours before each injection, during the fever, and 24 hours after the temperature increase. The total proteins were studied on the refractometer before, during, and after the fever, for each milk injection. Finally, the modifications of the glycemia and the proteinic fractions of the serum were examined by electrophoresis before, during and after the fever for each milk injection.

Comment: There is still some question as to the value of fever therapy in the nonspecific treatment of a variety of ocular inflammations. The research work of Dr. Vancea and his co-workers demonstrated that foreign protein injections can produce chemical changes which are not the same as those induced by steroid therapy. The specific importance of these biochemical changes in ocular therapeutics has not been demonstrated. Nevertheless, until we are absolutely certain of exactly what fever therapy does, further studies and further clinical evaluation are certainly justified. It does not seem that this form of treatment is ready for discard.

IRVING H. LEOPOLD

NEURO-OPHTHALMOLOGY

THE CHOLESTEROL AND CHOLESTEROL ESTER CONTENT OF CEREBROSPINAL FLUID IN PATIENTS WITH MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES

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Cumings (Brain, 1953, *76:* 551; 1955, *78:* 554) showed that demyelination of the human brain caused by multiple sclerosis resulted in a loss of free cholesterol and the appearance of cholesterol esters in the involved areas. A procedure for the accurate determination of small amounts of cholesterol and cholesterol ester in the cerebrospinal fluid was devised. This was based upon a new method for the extraction of cholesterol and a new technique for separating free and esterified cholesterol by silicic acid column chromatography.

The cholesterol and cholesterol ester content of the cerebrospinal fluid was determined in 6 normal individuals, 13 patients with multiple sclerosis, and 34 patients with other neurological diseases. Since it was desirable to perform the cholesterol analysis on 10 ml. of cerebrospinal fluid, it was difficult to survey a large number of normal individuals. The total cholesterol content in the cerebrospinal fluid of 6 patients diagnosed as neurotics with no neurological disease averaged 0.33 mg. per 100 ml., ranging from 0.26 to 0.43.

While levels of free and esterified cholesterol were raised in the cerebrospinal fluid of patients with a variety of neurological diseases (for example, free cholesterol ranged from 0.18 to 0.35 mg. per 100 ml. in patients with a convulsive disorder, while the ester varied between 0.14 and 0.26 mg. per 100 ml. in this group), only multiple sclerosis patients were characterized by a proportion of ester which was over 60 per cent of the total cholesterol. This finding correlates well with previous investigations of demyelinated tissue by Cumings. It is concluded that the determination of the percentage of esterified cholesterol in the cerebrospinal fluid is a promising adjunct in the diagnosis of multiple sclerosis.

Five patients with multiple sclerosis had cholesterol ester levels in excess of 60 per cent of the total cholesterol. Of the 40 patients bearing other diagnoses (including the 6 normals), none had more than 60 per cent of the total cholesterol as ester, and only 1 had a level of 60 per cent. The percentage of ester also correlated best with the degree of functional deficit possessed by individual patients with multiple sclerosis. However, 1 patient who had the largest amount of choles-

terol in ester form had a mild illness with retrobulbar neuritis as the chief manifestation.

The γ-globulin concentration was elevated in 7 of the patients with multiple sclerosis.

The data are insufficient to establish a correlation between the cerebrospinal fluid results and the activity of demyelination; more patients must be studied. An extension of the series is also desirable since the low γ-globulin levels of several of the multiple sclerosis patients are contrary to previous experience in the Georgetown University laboratory and may indicate that this group was not fully representative of the disease. If further studies now in progress confirm the present report, the determination of the percentage of esterified cholesterol in the cerebrospinal fluid may prove to be a valuable diagnostic aid.

The human brain, and especially the white matter, is rich in cholesterol which may be released into the cerebrospinal fluid. It is not surprising that destruction of brain or spinal cord tissue by various disease processes was accompanied by an increased cholesterol content of the cerebrospinal fluid. Increased levels of both free and esterified cholesterol were found in the cerebrospinal fluid of patients with cerebral infarction, brain tumor, and head trauma, and multiple sclerosis.

Comment: Any new laboratory adjunct to the possible diagnosis of multiple sclerosis should attract our attention. The fact that only the multiple sclerosis patients showed a proportion of cholesterol ester of over 60 per cent of the total cerebrospinal fluid cholesterol might be useful in certain neuro-ophthalmologic patients. However, all the cases cited in the study were well developed, with a history of remission and exacerbation, and with evidence of dissemination of lesions. Since the cholesterol content of the cerebrospinal fluid is apparently an indicator of the extent of demyelinization, it is unlikely that an acute retrobulbar neuritis in which multiple sclerosis is suspected would produce sufficient change for diagnosis. Since the authors state that 10 cc. of cerebrospinal fluid are essential for the test it is doubtful that this will be acceptable for a routine procedure in the differential diagnosis of optic neuritis. However, we will await further reports with interest.

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INJECTION THERAPY OF TIC DOULOUREUX

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Tic douloureux or idiopathic trigeminal neuralgia occurs more frequently in the middle-aged or elderly person, and affects women twice as often as men. In its typical form, it consists of a tic, *i.e.*, muscular twitching of face and a severe,

paroxysmal, agonizing pain which occurs in the distribution of one or more branches of the trigeminal nerve. It should be noted, however, that tic is not a constant feature of this condition; it is more often absent than present in trigeminal neuralgia. Typically successive brief paroxysms of pain occur, each lasting for not more than a minute. Signs are completely absent on physical examination. Spontaneous recovery is rare, but natural remissions of a duration of days, weeks or months may occur, especially during the early phase.

In the early stages medical treatment with simple analgesics, sedatives, antianemic medicines, vitamin B_1 and vitamin B_{12} may be tried. But eventually the sufferer will perforce seek surgical intervention. Surgical treatment, either by alcohol injection of the Gasserian ganglion, or II or III division of the 5th cranial nerve, or by open operation of trigeminal ramisectomy, offers outstandingly good results. The injection treatment with alcohol should be tried in every case, so that the patient can decide if the resulting numbness of the face is preferable to the pain.

The effect of the alcohol injection of the III or II division lasts for 6 months to a year, whereas that of the Gasserian ganglion lasts 2 to 3 years. The injection treatment should be repeated, especially in aged and debilitated patients; in some patients the neuralgia stops recurring after three, four or five effective injections. If the patient is in good general condition, open operation and division of the sensory root of the trigeminal nerve is the treatment of choice, since it gives permanent relief from pain.

The procedure of injection therapy is the only one discussed in the present paper; it demands a high degree of skill and should not be attempted by an occasional operator. In the mandibular division, the lateral route of Harris is safest. In the maxillary division, the needle is inserted in the angle between the coronoid process of the mandible and the lower border of the zygoma. For alcohol injection in the Gasserian ganglion two alternative routes are used. In using Harris's lateral route, about 0.8 cc. of 90 per cent alcohol is injected drop by drop, watching meanwhile for dilatation of the pupil and testing the eye movements, in order to stop the injection at the slightest sign of ocular paralysis. Should ocular paralysis take place, it is usually transient, with recovery at any time between a few hours and 5 months. Hartel's anterior route is the method of choice for injecting the Gasserian ganglion.

After injection of the Gasserian ganglion, neuropathic keratitis may occur due to diminution of lachrymal secretion. As a precautionary measure the eye must be protected by strapping a watch glass over it for at least 6 weeks, by which time the secretion of tears usually becomes normal.

The common practice among neurosurgeons today is to do fractional resection of the sensory root of the trigeminal nerve for patients with tic douloureux limited to the second or third division or to the lower two divisions as this gives lasting relief from pain without incurring the risk of an anesthetic eye.

Sixty-eight patients were treated for trigeminal neuralgia in the Department of Clinical Surgery of the King Edward Medical College, Lahore, from November to June, 1955, and end of May, 1956, to end of December, 1958. Sixty-four of

them were treated by alcohol injection, 6 cases with peripheral neurectomy and 11 cases with Frazier's trigeminal ramisectomy, with no mortality.

An occasional case may defy successive attempts at alcohol injections, and will have to submit to trigeminal ramisectomy, which will give him permanent relief.

Comment: Although it is not the place of the ophthalmologist to suggest forms of treatment to the neurosurgeon, one point made by the author is of considerable importance. He believes that alcohol injection should be tried in every case of trigeminal neuralgia in order that the patient can decide if the resultant facial numbness is preferable to the pain. This would have been desirable in a number of patients I have seen who bitterly resented the facial anesthesia for which they were not adequately prepared. It is unlikely that they would want their pain back either, but at least a choice might have been possible. It is interesting to note that the author lists the same ocular complications of maxillary branch injection as one sees after selective rhizotomy, namely ocular palsies and neuropathic keratitis.

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MUSCLES

A NEW TYPE OF TENDON TRANSPLANT OPERATION FOR ABDUCENS PARALYSIS

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The operation for abducens paralysis has two main component problems that must be solved in order to obtain a good result. The first and principal one is in balancing the pull of the internal rectus muscle against that of the externus; the second is in strengthening the abducting power of the eye by transplantation of the superior and inferior recti so as to enhance their secondary function of abduction. If the paralyzed eye cannot move spontaneously to the midline when both eyes are directed to the paralyzed side, a preliminary recession of the internal rectus muscle is indicated, or such a recession may be needed at a later operation.

Unless the main problem of lateral balance is solved in each individual case, the tendon transplant operation is doomed to failure. In the author's opinion, the use of the forced duction test is of great help in arriving at a decision, and if at operation the eye rotates easily in both lateral directions the second step of the operation (tendon transplant) may be carried out.

In the author's procedure, instead of splitting the superior and inferior rectus tendons, all that is necessary is to transplant the intact tendons midway between the lateral and vertical rectus muscle insertions. A double-armed No. 00000 chromic catgut suture is passed through the tendon in the following manner: First a central bite is taken and a square knot made, tying the central fibers; then each arm is threaded through the sides and a whipstitch taken at each border. This type of suture is also used on the lateral recti, for either recession or resection. Transplantation of the entire tendon offers the following advantages over splitting the tendons: (1) It is much more easily performed; (2) it is less hazardous, because the very thin halves of the tendon may conceivably tear during the operation; (3) it maintains the integrity of the tendons; and (4) the secondary abduction function of the vertical recti is greatly enhanced.

This technique has been used in two operations, in neither of which did vertical imbalance occur and in each of which the paralyzed eye could abduct and adduct 30 arc degrees after the operation (60 degrees in all). A review of the English literature showed that at least two other investigators, Hildreth and O'Connor, experimented with this idea before it occurred to the author. O'Connor's results were variable, and "a marked vertical deviation" obtained in the last case led him to abandon the procedure in favor of transplanting the medial

thirds. There is a good possibility, however, that this vertical deviation might have occurred no matter what type of transplant was used. It is not always possible to state before operation whether a patient has hypertropia or not, since the eyes cannot be examined in all cardinal directions of gaze. A latent vertical deviation might, therefore easily become manifest after ability to move the eye toward the paralyzed side was secured. Consequently, since vertical action is not necessarily affected, as shown by the author's two cases, it seems that the many advantages of the simplified procedure make it the operation of choice.

Comment: Before indicting the lateral rectus muscle or its innervation as the cause of a congenital lack of abduction, one should eliminate two other causes. The first cause is seen in cases of congenital esotropia where the child cross fixates with the adducted eye to look in the opposite direction thus eliminating the necessity to abduct either eye. On testing in the office one may be unable to elicit abduction of either eye. With alternate occlusion the child must use one eye to look in all directions and in such an instance full abduction of each eye may be rapidly achieved. The second cause of limited abduction is a thick inelastic medial rectus muscle or abnormal check ligaments about this muscle that keep the eye from abducting. This can be diagnosed by the forced duction test in which there is limited abduction on passive rotation of the eye. This may be primary or secondary to a paretic lateral rectus muscle. In either event the treatment of choice is first to sever the abnormal check ligaments and to recess the medial rectus muscle.

In cases where the eye rotates freely in the forced duction test the first treatment should still be a recession of the antagonist medial rectus combined frequently with a resection of the lateral rectus muscle. The resection should be avoided in Duane's retraction syndrome as shortening the fibrotic lateral rectus merely aggravates matters. Only after this treatment has failed to give a satisfactory result should one consider any of the tendon transplantation procedures. The critics of these procedures correctly question their effectiveness when they are combined with surgery on the horizontally acting muscles. The author has failed to answer these critics in that in his first case the result was disappointing until the medial rectus was recessed, and in the second case the vertical recti transplantation was combined with horizontal muscle surgery at the same sitting. This is too bad as the operation described appears to be superior to the tendon splitting procedures as it is simpler, and according to the work of Chamberlain in monkeys, is more efficient. The fact that no vertical imbalance was introduced is encouraging as that had caused O'Connor to abandon full tendon transplantations. The reviewer hopes that the author will use this procedure alone to see if in a larger series it can be more accurately evaluated.

PHILIP KNAPP

REFRACTION

WHAT IS TO BE EXPECTED OF AMBLYOPIA-TREATMENT?

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Ophthalmologica, 1959, *127:* 365–371

Fixation is one of the aspects of amblyopia that accompanies strabismus. In the majority of cases this fixation seems to be centric, independent of the visual acuity. In a small percentage it is either entirely absent, roving or nystagmoid near the foveola, or fixed eccentric.

It is the author's point of view that the fixed eccentric fixation is not susceptible of improvement. From a statistical analysis it seems likely that this form of amblyopia is found in stabismus convergens which began either at birth or in the first years of life. The form of amblyopia which is not accompanied by a fixed eccentric fixation is quite different.

The serious forms of amblyopia are predominantly found in cases of strabismus convergens. In 375 convergent squinters the author found 173 serious amblyopias (visual acuity less than 0.1), or 46.1 per cent; in 28 divergent squinters only 3, or 10.7 per cent. It seems that when squinting starts early, the frequency of serious amblyopia is greater.

With the purpose of gaining more insight into the prognosis of amblyopia treatment in monocular strabismus convergens, a statistical analysis of a number of amblyopias with a centric fixation was made; these were cases treated during one year passively or actively. The material was therefore divided into groups (171 treated children younger than 10 years of age), according to the onset of strabismus. Without statistical analysis it also appears that the full visual acuity was never obtained.

In all cases except in those with fixed eccentric fixation an attempt to improve the visual acuity of the amblyope is justified. The visual acuity of the amblyopias with strabismus convergens rises as far as 10/10 in very few cases only. The refraction has little to do with the genesis of the strabismus convergens.

In the reported analyses the seriousness of the amblyopias at the start of treatment was not discriminated. Thus the possible favorable result which Bangerter (*Amblyopiebehandlung*, Ed. 2, 1955) mentions with slight amblyopia, did not emerge. However, the data show that in all circumstances it is justified to start amblyopia treatment.

Another accompanying phenomenon of strabismus convergens, namely the abnormal correspondence, ought to be prevented. This mostly appears at the beginning of strabismus convergens and is a serious obstacle in orthoptic train-

TABLE I

Average Visual Acuity (171 Cases)

No.	Duration of Affection	Before Treatment	Improvement	After Treatment
	yr.			
20	Less than ½	0.20	0.38	0.58
26	½-1	0.15	0.41	0.56
38	1-2	0.14	0.43	0.57
25	2-3	0.17	0.37	0.54
19	3-4	0.19	0.34	0.53
19	4-5	0.12	0.38	0.50
24	More than 5	0.24	0.31	0.55

ing. In order to avoid this complication, amblyopia treatment should be begun early and continued, even if the visual acuity of both eyes is the same.

Comment: One of the more common frustrations in the practice of ophthalmology begins something like this. A school nurse tests the visual acuity of a 7-year-old child, and finds O. D. 6/6, O. S. 6/60. The parents receive a slip notifying them that their child has defective vision and that this should be corrected. When the child is examined, the ophthalmologist finds a large anisometropia, with amblyopia of the left eye. The eyes are straight, thanks to good peripheral fusion. He hesitates to patch the better eye, for fear of precipitating a squint. Furthermore, because of the age of the child, treatment of the amblyopia would be long, costly and uncertain of success.

The ophthalmologist writes a note stating that in this case it is best to leave the child alone. The parents may be satisfied, but the school authorities may not. When the next physical examination is done, they note that whereas the other defects found, such as teeth and infected tonsils, have been eliminated, the vision of the left eye is still 6/60 and ergo has been neglected. A stiff note demanding better attention is sent to the parents who now come flying distraught to the ophthalmologist's office.

This happens to the eminent as well as to the obscure opthalmologist. At a recent Academy Meeting, one of the leaders of American Oopthalmology, in a casual lobby conversation, complained bitterly of his inability to get school nurses to trust his judgment.

The usual health program of the school as it relates to the eye proceeds in blithe disregard of the concept of visual maturity. It begins its laudable attempt at preserving vision at the very age when the visual habits of the child are solidified. The golden period from 2 to 6 years of age when the child is most plastic and responsive to treatment has been lost forever. The schools are frantically trying to lock the stable after the horse has been stolen.

The limited benefit of such programs is shown by the fact that amblyopia exanopsia is still the largest single cause of uniocular visual disability. No doubt, pleoptics will salvage some of these cases. To make such treatment universally available would require a vast outlay of time and money, and might take many years.

To quote Parks[1] "Pleoptics can definitely give a good result sooner than simple occlusion and homework exercises, but the question is raised as to whether it is justified. The final outcomes of the two methods are not outstandingly different, but even Bangerter states that a child of five or six years requires anywhere from twenty to one hundred and twenty treatments but with the occlusion method, even if the child saw the orthoptic technician

every two weeks over a six month period he would make only twelve visits. So the old-fashioned time proved method of early and total occlusion is far from being abandoned. I think that with simple occlusion at an early age, plus mass visual screening of all children between four and four and a half years of age, there would result within one generation such a scant number of monocular amblyopes of the exanopsia type that little need would prevail for these expensive and noble attempts to improve amblyopia at a later time in life."

Ophthalmologists should take steps to set up such screening programs for preschool children in their own communities. This might be done by requiring registration for the first grade to be done 2 years in advance.

Techniques for mass screening of 4-year-old children should not be too difficult to devise. We ophthalmologists are the ones who possess the specialized knowledge, and it is our responsibility to transmit this knowledge to those working in the field of School and Public Health.

OWEN BELMONT

REFERENCE

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RETINA

DETACHMENT OF THE RETINA

EDITORIAL

Brit. M. J., 1959, *April:* 1097

The last decades have seen two major advances in eye surgery. Corneal grafting has had ample acclaim, and its problems have been aired on the stage, cinema screens, television, and even in Parliament. But the other great surgical triumph, that of mastering retinal detachment, has probably saved more eyes from blindness even than the perfection of corneal-grafting technique. The pioneering work in both of these fields by Professor Louis Paufique, of Lyons, is well known far outside the world of ophthalmology, and in electing him as Bowman lecturer for 1959 the Ophthalmological Society of the United Kingdom added its well-merited tribute.

For his Bowman lecture, delivered earlier this month in London, Professor Paufique reviewed the present status of the treatment of retinal detachment, first looking back to the days of his youth, before Gonin had performed his first successful repair by use of the Paquelin thermocautery. Even in 1929 Professor Gayet had declaimed, "To wish to treat a retinal detachment, one must be either a charlatan or a fool." After the uncertain results with the cautery came Weve's introduction of the safer and more reliable diathermy and improved methods of localizing the retinal tears by transillumination. In 1950 the more difficult and dangerous full-thickness resection of Muller and Lindner began to be replaced by lamellar scleral resection. This last operation has been elaborated, particularly by C. D. Shapland in England and Paufique himself in France, and nowadays is the operation of choice in about half the cases of detachment of retina. Still more recent advances have included the transplantation of vitreous and coagulation by light[1]: these procedures now have their established place in a small percentage of cases.

Reviewing his last 524 cases, Paufique recorded successful results in 70 per cent—a figure which corresponds with most other recent assessments. In about half of the failures the nature of the detachment could be said almost to have precluded cure, but it is still difficult to find an adequate explanation for failure in the remaining 15 per cent. Paufique therefore cast about for other factors in the pathogenesis of such detachments, and among the various possibilities he presented impressive histological evidence of certain congenital choroidal lesions which might well be responsible and so warrant prophylactic surgery. Discussing treatment, he stressed the value of the injection of lyophilized vitreous, which can readily be stored as a powder, and of coagulation by light. The place for preventive treatment, especially the use of epichoroidal galvanocautery, is still debatable.

[1] See annotation, *Brit. Med. J., 2:* 1345, 1958.

EXTERNAL DISEASE

CONTACT DERMATITIS FROM 4-TERTIARY BUTYL CATECHOL IN THERMO-FAX PAPER

Report of a Case

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New England J. Med., 1959, *260:* 1076–1078

Dermatitis that appeared in a 22-year-old woman as a result of handling Thermo-Fax paper has been shown to be due to the 4-tertiary butyl catechol contained in that paper as it was manufactured before 1958. Previous reports by other workers that noted a sensitivity to this duplicating paper, and four of which indicated that 4-tertiary butyl catechol might be the offending agent, have thus been substantiated.

The patient's chief complaint when she was first seen was of an itching eruption that appeared on examination as patches of bright papular erythema on the medial aspect of the right forearm and similar but faint patches on the left forearm, the front of the neck, and the right side of the face. She continued at work while being treated. When she was seen 13 days later, the eruption had become more widespread and severe; circinate lesions were evident on the face and neck, and there was lichenification on the right eyelid. Absence from work led to some improvement, but a return to work was followed by exacerbation of the dermatitis, with puffy eyelids and erythema of the forearms. Patch tests indicated sensitivity to Thermo-Fax paper, with which she had rarely been brought in contact until 6 weeks before her initial examination. A change in duties at that time had obliged her to handle this paper some 85 times a day. By wearing long-sleeved dresses and white-cotton gloves for protection, she was eventually able to resume full-time work without ill effects. At follow-up a year and a half later, she was found to have been working steadily and to have kept free of inflammation if she was cautious when touching the duplicating paper. At this time, she was tested with a square of Thermo-Fax paper from the sheet to which she had originally had a reaction, with the Thermo-Fax paper in current use in her office, and with a new modification of the paper. Positive reactions were obtained with the paper containing 4-tertiary butyl catechol and with an inert base to which this chemical alone had been added. No reaction followed tests with the duplicating paper from which only 4-tertiary butyl catechol was omitted. Paper for some of the tests was supplied by the manufacturer and officials of the company thus helped to demonstrate that the allergenic component of the paper used by the patient was 4-tertiary butyl catechol. This chemical is no longer contained in Thermo-Fax

paper, but since its use in industry is widespread, physicians should be alerted to the fact that for certain persons it is an allergen.

Comment: Eyelids may share in the allergic reaction to 4-tertiary butyl catechol which is in widespread use in industry. This patient demonstrated lichenification of the right upper lid as well as puffiness of all lids. Sometimes it is difficult to find the offending allergen, and here is another compound which must be kept in mind.

IRVING H. LEOPOLD

ASSOCIATION OF ADENOVIRUS TYPE 8 WITH EPIDEMIC KERATOCONJUNCTIVITIS

SPECIAL REFERENCE TO THE INFANTILE FORM OF THE DISEASE

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A.M.A. Arch. Ophth., *61:* 891–898, 1959

Isolation of adenovirus type 8 from epidemic keratoconjunctivitis (EKC) in Japan supports the impression that EKC is an etiologic entity caused by this adenovirus, and provides laboratory evidence for differentiation between EMC and pharyngoconjunctival fever (PCF).

Thirty-eight strains of adenovirus type 8 were isolated from 49 cases of clinical EKC seen at the eye clinic at Kumamoto, Japan, between May 1956 and June 1958. They were isolated from 12 cases of typical EKC (adult), 12 cases of probable EKC (adult), 2 cases of unidentified EKC (adult), and 12 cases of infantile EKC. Examination of paired serums from 35 cases revealed in every instance a definite rise in neutralizing antibody to type 8 virus during the illness.

The isolation technique is described. During the first 5 days of the conjunctivitis, virus isolation was successful in 80 per cent of the attempts; isolation became more difficult during the 2nd week, and was not accomplished after the 10th day. Conjunctival scrapings were the best material for virus isolation, conjunctival washings or discharge proving unsatisfactory.

Virus isolation was also attempted in 4 cases of clinical PCF; 2 cases were from epidemics and the other 2 were sporadic and were diagnosed as "probable PCF." Three cases yielded type 3 adenoviruses and the 4th case type 1. In each instance a rise in the specific neutralizing antibody to the homotypic virus occurred during the illness. There were definite systemic symptoms in all cases but no keratitis. Six additional cases from a moderate sized epidemic of PCF in July and August, 1956, showed a high neutralizing antibody titer to adenovirus type 3, and, except for 1 case, no antibody to type 8.

According to the clinical observations, supported by virus isolations and anti-

body studies, EKC and PCF can easily be differentiated from each other in epidemics. In EKC, subepithelial punctate keratitis appears in about one-half the adult cases. In PCF such a keratitis is rare and atypical. In EKC, systemic symptoms, though common in infants, are rare in adults and always milder than the systemic symptoms of PCF. In sporadic cases the differentiation of EKC from PCF is often difficult. In adults the appearance of typical subepithelial opacities indicates the diagnosis of EKC caused by adenovirus type 8 infection. If definite systemic symptoms are observed, PCF should be suspected. However, if both keratitis and systemic symptoms are absent it may be impossible to differentiate the two entities by clinical examination. Virus and serologic studies are required for the accurate diagnosis of such cases.

In infants less than 2 years of age infection by adenovirus type 8 usually manifests itself as a pseudomembranous conjunctivitis. Keratitis and preauricular adenopathy are rare, but some systemic symptoms occur in about one-half of the cases. The systemic symptoms tend to be considerably milder than those of PCF.

EKC is definitely known to be transmissible in swimming pools. A swimming pool epidemic of conjunctivitis, therefore, does not necessarily support the identity of the disease with PCF as has been assumed in the United States.

Additional observations along the lines of this study can be expected to aid further in establishing EKC and PCF as different etiologic entities.

Comment: This is a solid contribution by experienced workers. It has practical value in terms of virus isolation technique, and adds to our understanding of the transmission and natural history of epidemic keratoconjunctivitis. The clinical picture of infantile EKC should be noted by ophthalmologists in the event of its appearance in this country.

HENRY F. ALLEN

SURGERY

ADVANCES IN CATARACT SURGERY

With Particular Reference to a New Technique of Subluxation and to Enzymatic Zonulolysis

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J. M. A. Alabama, 1959, *28:* 365–371

Three major problems confront the surgeon in every proposed operation for senile cataracts. The first is the general status of the patient; particularly important is his cardiovascular status. The second is the timing of the operation. The third is the selection of the procedure. In senile cataract the most favorable time for surgery has arrived when the patient evidently needs it. With the development of the intracapsular technique, the visual needs of the patient rather than the precise maturity of the cataract set the time for surgical intervention.

If the cataract is monocular, there is sometimes a temptation to postpone operation. The temptation should be resisted. Delay is not wise for three reasons: (1) Binocular vision is safer and more efficient than monocular vision. (2) The longer the operation is deferred, the more advanced is the age of the patient, and the more likely are systemic diseases and their complications to be present. (3) The sooner the operation is performed, the less is the risk of the complications often associated with cataract, chiefly secondary glaucoma and iritis arising from hypermaturity. This is the most important reason of all for prompt surgery.

If the cataract is bilateral, the question of operation on the second eye arises after operation on the first. Again, particularly when a good result has been obtained, there is sometimes a temptation to let well enough alone. This is another temptation which should be resisted. In the author's opinion, the second operation is mandatory, unless some serious contraindication to surgery has developed which would justify a delay.

In spite of the advances in cataract extraction in the last half century, a number of problems remain to be solved. Many of the earlier problems were eliminated when the intracapsular technique was introduced, but the extracapsular technique is still the preferred operation under certain conditions, such as the management of hypermature cataracts with liquid cortical material, in cataracts in which the vitreous is fluid, and in cataracts associated with an old iridocyclitis with adhesions. Whenever there is a narrowing of the chamber angle when the eye is opened, the use of the extracapsular technique may prevent loss of vitreous that is already bulging forward. When the intracapsular operation is used, the entire lens is removed within its capsule and no particle of lens material is left

behind to cause inflammation and swelling and thus lay the groundwork for iridocyclitis and secondary glaucoma. Both operations have their disadvantages.

Even when the extracapsular technique is used on strict indications, the remaining posterior lens capsule may become opaque. The intracapsular technique has resulted in more frequent loss of vitreous which is always an invitation to retinal detachment. Any disruption of the anterior vitreous face as a result of added pressure during the operation may allow the vitreous free access to the iris, with subsequent inflammation, direct blockage of the chamber angle, and the formation of corneal adhesions.

A new technique is also described which, in an extensive experience, has proved efficient as well as free from the objections of the earlier techniques. It is a technique of subluxation which has reduced the incidence of capsular rupture to a minimum because it reduces the amount of traction on the lens capsule and eliminates the use of a vitreous wedge for subluxating the lens. The usual adequate corneoscleral section is made and the usual corneoscleral sutures are placed. Then a broad instrument, either a lens spoon or a lens loop, is placed on its side just behind the posterior lip of the incision and in the 12 o'clock position. When slight pressure is exerted with the instrument against the posterior lip, the pressure is transmitted by the lip itself, with its shelf, to the superior equator of the lens. As a result, the lens is caused to tilt along a transverse axis, feet up, and there is a very slight deformation of the vitreous body. The pressure applied is just enough to produce stretching of the suspensory ligament inferiorly, but not enough to produce a vitreous wedge intended to rupture the ligament. If a limbal-based conjunctival flap has been used, it can be smoothed back over the sclera and the spoon or loop applied over the region of the incision to produce a better tilt of the lens.

Point pressure, combined with a sliding movement, is now applied with the muscle hook just within the corneal margin, from 5 to 7 o'clock. The lens loop is next moved clockwise to the 2 o'clock position and the muscle hook is manipulated with the same point pressure and sliding movement to rupture the zonular fibers in that area. Finally, a similar maneuver is carried out with the lens loop at 10 o'clock, while the muscle hook is moved between 4 and 6 o'clock. If the zonular fibers are not resistant, the lens can be subluxated inferiorly by this technique. If no rupture of the inferior fibers is evident at the end of the manipulations described, the chances are that this technique will not succeed. The best plan then is to resort to stripping of the zonular fibers under direct visualization by the Kirby method.

Zonular rupture by capsular traction alone, as the early experiences showed, is a difficult and uncertain method of accomplishing subluxation of the lens. Delivery of the lens can be accomplished either by the sliding method, with the superior pole first, or the tumbling method, with the inferior pole first. The author's preference is for the tumbling technique when conditions permit it.

In view of the difficulties just described in securing rupture of the zonular fibers in cataract extraction, it is easy to see why any measure which will expedite this step would be welcome. It may be that the answer has been found in a pro-

cedure termed enzymatic zonulolysis, but a personal experience with α-chymotrypsin suggests that, while it is highly effective, it also has some dangerous side effects. Until its innocuousness is also proved by a series of carefully controlled studies, both experimental and clinical, it should be used with caution. Disastrous results could be associated with its use in children. Uveitis may follow the use of an incorrect concentration of the enzyme. Since this is a proteolytic enzyme, it may induce an allergic response in the operated eye which will not be evident until the second eye is operated on by the same technique. Studies must be carried out to determine its effect on the cornea, the iris, the iris angle and the hyaloid membrane. Until then definitive statements about the limitations and risks as well as the advantages of enzymatic zonulolysis will not be possible.

Comment: One of the more desirable features of writing for the SURVEY is that the reviewer or commentator can express his own opinions. This reviewer takes definite exception to the statement that patients with monocular cataracts should be urged to have surgery performed. In the presence of the threat of lens induced glaucoma, mechanical or toxic—yes; otherwise, the needs of every patient should be carefully evaluated.

Binocular vision is better and safer than monocular vision but a large percentage of our older patients cannot handle a contact lens or do not have the patience to persist with it, especially if they have normal vision in one eye. The other possibility is the plastic insert and even though the posterior chamber lenses are still popular in this area the reviewer has not yet succumbed.

The health of the patient should, of course, be taken into consideration but since most patients can, if necessary, be out of bed within a few hours after an operation we need not fear the risks of immobilization.

In the reviewer's opinion, some of his most disgruntled patients are those with unilateral aphakia and workable vision in the phakic eye. The exceptions are those who have to have binocular vision for their employment or who demanded the surgery and have the motivation to try and persist with a contact lens. Some surgeons avoid these complications however by operating on both eyes at the same period of hospitalization. The adjustment to binocular aphakia, be it precipitous or not, is probably easier than to monocular aphakia.

The reviewer feels than one cannot be dogmatic about the patient with a monocular cataract. Every patient has a different problem and if they are warned of the symptoms of hypermaturity and can be seen twice a year their chances of getting into trouble are not great.

P. ROBB MCDONALD

POSTOPERATIVE CHOROID DETACHMENT

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Ophthalmologica, 1959, *137:* 436–441

In the postoperative complication of choroid detachment, the development of one or more round grayish-brown vesicles is seen, starting from the periphery of the fundus, with a smooth surface and without undulations. When there are several bladders, they are usually sharply demarcated and the normal fundus is visible between them. The anterior chamber of the eye is often shallow or nearly abolished. The vesicles may become so large that they touch each other behind the lens.

Experience has taught that the majority of these detachments disappear spontaneously in a few weeks without leaving any trace. It is not necessary to keep patients with this complication hospitalized. However, some cases show a progressive course. Detachments developing more than three weeks after operation also show less tendency to disappear spontaneously. Apart from the risk to the retinal function, the prolonged existence of extensive choroid detachments causes a feeling of discomfort both in the patient and in the ophthalmologist, who observes no improvement, or even a progression.

The incidence, in the author's experience, was 10 out of 206 cataract extractions (5 per cent) and 2 out of 27 Elliot-trephinings.

Whatever the mechanism of the development of choroidal detachment may be, the rapid and complete restoration following drainage of the subchoroidal fluid is a striking phenomenon. Apparently, a vicious circle in the form of a disturbance in the intraocular relationships regarding pressure and fluid between anterior chamber, perichoroidal space and vitreous body, is interrupted by the interference of the ophthalmologist. If wound leakage is assumed to be the primary factor, the detachment can be treated by closing the wound by resuturing or diathermy. This is less simple than diascleral puncture which the author prefers.

Comment: The pathogenesis of choroidal detachment is still a mystery. As a rule, one does not look for it unless one has a shallow anterior chamber, at other times it may be seen grossly with a flashlight when the chamber is of normal depth.

The only factor we are sure of is that it is associated with decompression of the globe. The reviewer also has the clinical impression that as far as cataract surgery is concerned it is more prevalent in those cases where rupture of the zonule has been difficult and has required considerable manipulation.

In the reviewer's opinion, in the presence of a leaking wound the chamber is not reformed at the first dressing or becomes shallow about the 7th to 10th day because of leakage around a deep necrotic suture tract. Correction of either defect usually leads to prompt reformation of the chamber.

In discussing this problem it is difficult to tell which comes first, the shallow chamber or choroidal detachment. There is a definite relationship between the two since the

chamber usually forms as the detachment subsides. The reviewer agrees that Diamox is of little value. The criteria used for surgical intervention (withdrawal of subchoroidal fluid and injection of air into the anterior chamber) are: (1) no demonstrable wound leak, (2) absence of the chamber for 48 to 72 hours (which is not due to vitreous block) or (3) contact of the vitreous or lens (in filtering procedures) with the cornea.

The procedure for releasing fluid and the injection of air is not difficult but precautions must be taken since this is usually done before there is secure healing of the wound.

The author does not mention choroidal detachment following surgery for retinal detachment. In appearance the choroidal detachment is the same as that following cataract surgery but if unsuspected and associated with a residual retinal detachment it may lead to the erroneous diagnosis of a tumor or unnecessary additional surgery for the retinal detachment.

P. Robb McDonald

SYSTEMIC DISEASE

DIFFUSE COLLAGEN DISEASES AND THEIR OCULAR MANIFESTATIONS

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Antiseptic, 1959, *56:* 29–44

The diffuse collagen diseases manifest in different degrees changes in connective tissue, including fibrinoid degeneration of collagen, excessive deposition of collagen, increase or alteration in ground tissue, proliferation of connective tissue with or without degenerative changes, and inflammatory cellular infiltration. In discussing the pathologic process of fibrinoid degeneration, the typical connective tissue lesion found in the collagen diseases, three principal aspects must be considered: (1) destructive, *i.e.*, swelling, loosening and disintegration, and breaking down of collagen fibers, the fibroblasts and the elastic fibers forming a necrotic debris giving the staining reaction of fibrin, to which is due the term "fibrinoid degeneration"; (2) productive, *i.e.*, proliferation of fibroblasts not necessarily in the neighborhood of the areas of degeneration but encroaching upon the necrotic mass when near; and (3) inflammatory, *i.e.*, reaction to the primary connective tissue injury. Each of these processes has a varying effect on anatomically different tissues, and it is to these variations that the diverse manifestations of the collagen diseases are essentially due.

The ocular manifestations are numerous in every collagen disease. Most of these lesions can be explained on the basis of the tissue affected and the pathologic change produced in it. For example, fibrinoid degeneration of the walls of the blood vessels will cause subconjunctival, intraocular, or retinal hemorrhages

and retinopathies, depending on the tissue in which the vessels are affected. They are more likely to be present in serum sickness, disseminated lupus erythematosus, anaphylactoid purpura, periarteritis nodosa, and thromboangiitis obliterans. In the same way, keratitis, scleritis, tenonitis, muscular palsies, and others are found when the collagen fibers of the structures concerned are affected concurrently with similar lesions elsewhere in the system, as in dermatomyositis, scleroderma, and mucocutaneous ocular syndromes. The commonest ocular manifestation in these diseases is chronic nongranulomatous iridocyclitis.

The fact that various ocular manifestations may appear in combination in a single case makes it impossible to correlate any particular ocular lesion with any particular type of diffuse collagen disease. The lesions that may be encountered, singly or in combination, in the different structures of the eye may be summarized as follows: (1) lids: edema, ptosis; (2) conjunctiva: chemosis, redness, conjunctivitis; (3) cornea: edema and hemorrhages; various types of keratitis; (4) sclera: scleromalacia perforans (seen in rheumatoid arthritis), scleritis, and episcleritis; (5) iris: nongranulomatous iritis with hypopyon in some case; (6) pupil: pupillomotor lesions; (7) lens: cataract; (8) vitreous: intraocular hemorrhages; (9) retina and optic nerve: toxic and hypertensive retinopathies, perivasculitis, detachment, thrombosis, embolism, and aneurysm of smaller vessels, neuritis, and papilledema; (10) visual pathway: thrombotic phenomena giving rise to hemianopsia; (11) Tenon's capsule: tenonitis; and (12) muscles: eotraocular palsies.

The principal diffuse collagen diseases are acute disseminated lupus erythematosus; polyarteritis nodosa, which is accompanied by a greater variety of ocular manifestations than any other collagen disease; rheumatoid arthritis, including Still's disease; rheumatic fever; serum sickness; thromboangiitis obliterans (Buerger's disease); dermatomyositis; scleroderma; erythema nodosum; erythema multiforme; Henoch's (Schonlein-Henoch) purpura; Reiter's syndrome; and various mucocutaneous ocular syndromes (Behcet's disease, Stevens-Johnson disease, and ectodermosis erosiva pluriorificialis), usually placed in the category of collagen diseases, though sometimes regarded as viral in origin; and temporal arteritis, which is of special ophthalmic importance, because the arteries of the optic nerve are involved in more than half the cases, causing rapid visual loss. Central artery occlusion, papilledema, and optic atrophy may also be caused by temporal arteritis.

Treatment of the ocular manifestations of the collagen diseases naturally varies with the various diseases; sulfonamides and antibiotics are valuable in some, while others respond best to hormone therapy with cortisone or ACTH.

Comment: This is an up-to-date review of the concept, the symptomatology and the treatment of the so-called collagen diseases.

If one assumes the factor of hypersensitivity as the basis for all these affections as the majority of observers do, some other conditions such as nodular nonsuppurative panniculitis (Christian-Weber Syndrome) which may also be associated with uveitis, and some more localized lesions such as idiopathic arteriolitis (Jensen's juxtapapillary retinopathy) might be considered as belonging to this group of diseases.

BERTHA A. KLIEN

OCULAR SARCOIDOSIS

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Am. J. Med., 1959, *26:* 331–339

The earliest descriptions of sarcoidosis drew attention to the cutaneous manifestations of the disease. Nearly 60 years were to elapse before it became accepted that the eye could be involved in a similar process. Finally uveoparotid fever was identified as but another manifestation of sarcoidosis. Any structure of the eye may be involved by sarcoid tissue. Erythema nodosum with bilateral hilar lymphadenopathy may be associated with ocular sarcoidosis.

Ocular lesions were observed in 50 of 200 patients with sarcoidosis. They included subacute or chronic iridocyclitis, conjunctivitis, keratoconjunctivitis sicca and conjunctival follicles. The differences between subacute and chronic iridocyclitis are striking. This is in part due to corticosteroid therapy, which has probably changed the natural history of sarcoid iridocyclitis.

The peak incidence at the onset of ocular symptoms lies in the 40- to 50-decade with a mean age at onset of 39 years. The range is similar to that observed for skin lesions. Sarcoidosis affects both sexes to about the same extent but in those patients with ocular lesions there was a conspicuous preponderance of females. Intrathoracic involvement occurred in 41 of 50 patients (82 per cent) with ocular disease. The changes ranged from bilateral hilar lymphadenopathy to diffuse pulmonary mottling without hilar gland enlargement. Skin lesions included lupus pernio, maculopapular eruptions, persistent plaques, scars or erythema nodosum. They occurred in one half of the series; the incidence was the same in the groups with and without ocular disease. Enlarged palpable lymph nodes were present at some stage of the disease in 50 per cent of patients with ocular disease, compared with 33 per cent of the group without eye manifestations. Kveim tests provided histologic evidence of sarcoid tissue in 129 of 149 patients. They were positive in 83 per cent of 36 patients with ocular sarcoidosis.

Histologic examination revealed well defined follicles composed of large pink-staining epithelioid cells, occasional giant cells, a thin peripheral ring of lymphocytes and inconspicuous central necrosis. The absence of caseation and of acid-fast bacilli and the preservation of the reticulin network served to distinguish it from tuberculous tissue. Apart from the results of the Kveim test, histologic evidence of sarcoid tissue was also found in various tissues by biopsy in 37 patients and at necropsy in one. Histologic confirmation of sarcoid tissue in the ocular series was obtained from skin in 12, lymph node in 8, liver in 7, enucleated eye and tonsil in 2 patients each, and once from nasal mucosa, parotid gland, lacrimal gland, palate, bone and breast. Reduced secretions due to simultaneous lacrimal and salivary gland involvement may superficially resemble Sjögren's syndrome. Histologic evidence should, whenever possible, confirm the clinical diagnosis.

The natural course of sarcoidosis is toward spontaneous healing by fibrosis. In the eye this may cause serious complications, so ocular involvement is an absolute indication for early and energetic corticosteroid therapy. In the present series 8 of the 11 patients with subacute iridocyclitis had received intensive corticosteroid therapy within a few weeks of the onset of symptoms. Six received local cortisone eye drops, and in two these were preceded by subconjunctival injections of hydrocortisone. Four patients received oral cortisone or prednisolone. In all instances, there was rapid relief from symptoms and subsidence of the signs of ocular inflammation without recurrence within 6 months. All other clinical and radiologic features of sarcoidosis had also cleared within 1 year.

In the group of patients with chronic iridocyclitis, corticosteroid therapy had been delayed for 1 to 14 years. Eventually cortisone was given locally or orally to 14 of these patients. Slight benefit was sometimes observed but the results of treatment were understandably disappointing at this late stage of irreversible ocular fibrosis.

Comment: Ocular sarcoidosis is an important disease in ophthalmology and unfortunately, although a number of the acute ocular manifestations will subside with steroid therapy, not all of them clear or remain quiet even with prolonged administration of these hormonal agents. The chronic varieties of the disease do not do well on this therapeutic approach. Other therapeutic approaches are necessary, and further studies along this line are mandatory. Recently the use of chelating agents has been introduced for this disorder, but it is too early to determine whether they will be any more effective than older forms of therapy.

IRVING H. LEOPOLD

RICERCHE SULLA SUPPOSTA IMPORTANZA DELLE CRIOGLOBULINE NEL DETERMINISMO DELLE OCCLUSIONI VASCOLARI E DEI FENOMENI EMORRHAGICI RETINICI

(INVESTIGATIONS ON THE SUPPOSED IMPORTANCE OF CRYOGLOBULINS IN THE DEVELOPMENT OF VASCULAR OCCLUSIONS AND HEMORRHAGIC PHENOMENA OF THE RETINA)

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Boll. ocul., 1958, *37:* 949–956

Occlusions of retinal arteries or veins may be divided into three groups from the pathogenetic point of view: (1) those due to external pressure on the vessel; (2) those due to alterations of the vessel wall itself; and (3) those due to alteration of the constitution of the blood.

A pathogenetic mechanism has recently been suggested for the third group, namely, the presence of cryoglobulins in the blood. Ellis (A. M. A. Arch. Ophth., 1957, *57:* 327) reported the presence of cryoglobulins in the blood of a patient with occlusion of the central retinal artery of the right eye and of the central retinal vein of the left eye. A search of the literature revealed that the presence of cryoglobulins in the blood was generally accompanied by vascular occlusions or more or less diffuse hemorrhages in the retina.

For a better understanding of the role this protein plays in vascular retinal occlusions, all cases of retinal vessel occlusions and some cases of retinal hemorrhage coming to the Eye Clinic of the University of Cagliari were tested for the presence of cryoglobulins. The subjects included 12 patients with occlusions of the central retinal vein, 5 with occlusions of the central retinal artery and 9 with retinal hemorrhages of an undetermined nature. All were otherwise "normal" with the exception of 12 (4 with hypertension, 1 with myocardiosclerosis, 2 with hypertension and myocardiosclerosis, 1 with myocardial insufficiency, 1 with myocardial insufficiency and hypertension, 1 with generalized arteriosclerosis, 1 with ectasia of the vessels, 1 with chronic rheumatism and pulmonary emphysema).

Five or 6 cc. of fasting blood were taken from the cubital vein and maintained at body temperature before and during centrifugation for 5 hours. The serum obtained from the centrifugation was placed in a refrigerator at 40°C. for 24 to 48 hours. It is important that the blood be maintained at body temperature during the centrifugation to prevent the cryoglobulins from precipitating together with blood particles. When cryoglobulins are present they form a whitish, cottony precipitate or coagulate in the serum samples after refrigeration. When the serum is again brought to body temperature the coagulate or precipitate dissolves.

Cryglobulins were not found in any of the samples although in several instances refrigeration was continued for 4 or 5 days. An increase of globulin was found almost constantly in the cases of occlusion of the retinal vein and more irregularly in the other cases.

The hemogenic tests were normal except in one case of retinal artery occlusion and two of retinal hemorrhage, one of which had marked capillary fragility.

It thus appears that the presence of cryoglobulins is not an important factor in the pathogenesis of central retinal vascular occlusions, except possibly in rare cases where the occlusions are accompanied by diffuse hemorrhagic alterations, phenomena of Reynaud's type and increased sensitivity to cold. It is pointed out that in the cases reported in the literature of cryoglobulinemia associated with occlusions of the retinal vessels or hemorrhagic lesions, these ocular alterations were not isolated but were part of a complex general symtomologic picture.

Comment: This report implies that cryoglobulins play no part in the pathogenesis of retinal vascular occlusions. This may very well be true. However, the cryoglobulin level may be highly variable in any one individual. In the patient with the central retinal artery occlusion, that I reported in 1957, the cryoglobulin level at one time was determined to be 1 gm. One year later during a hospitalization, cryoglobulins could not be

found in this patient. Small amounts of cryoglobulins require longer periods of time in refrigeration for precipitation to occur. Therefore keeping all specimens in the icebox for one week may alter the results. Cryoglobulenemia is thought to be a nonspecific indication of some disease process. Its presence may stimulate further study of the patient in search of the etiology of the underlying pathology. The role of cryoglobulins in retinal occlusions may be minor and insignificant. However the laboratory test is simple and inexpensive and worth performing in obscure vascular occlusive cases.

RICHARD A. ELLIS

ORBIT

OCULAR ASPECTS OF ENDOCRINE EXOPHTHALMOS

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Illinois M. J., 1958, *114:* 226–229

The ocular signs of Graves' disease are familiar to every physician, so that the ophthalmologist is rarely consulted concerning their management. The clinician is well aware of the ocular problems that may be caused by sudden depression of thyroid activity and directs his therapy in a manner calculated to produce minimal disturbance of the orbit. The widespread use of diagnostic methods to determine thyroid function and the kinetics of iodine metabolism have virtually eliminated blindness caused by malignant exopthalmos.

Usually, the thyroid abnormality may be controlled but the eye signs give rise to cosmetic and visual problems, particularly in women. Patients requiring ophthalmic care fall into three groups:

1. Those with acute thyrotoxicosis with eye signs that dominate the clinical picture.
2. Those with ocular signs of thyroid disease without history or evidence of past or present thyroid abnormality.
3. Those with aggravation of the ocular signs following effective therapy of thyroid abnormality.

In each group a unilateral ocular protrusion would direct suspicion toward neoplasm or inflammation, rather than systemic disease. The distinction between thyrotropic and thyrotoxic types of exophthalmos is believed by many to be unjustified.

In the first group, that of acute thyrotoxicosis with predominantly ocular signs, the signs may be dominated by congestive features; edema of the lids and conjunctival congestion are prominent. Patients whose disease is ushered in with orbital edema are particularly prone to develop the permanent crippling effects of endocrine exophthalmos: optic nerve involvement with changes in the visual fields, glaucoma, muscle palsies, and orbital stasis with an incompressible exophthalmos.

The occurrence of characteristic eye signs of hyperthyroidism in patients who demonstrate no signs of hyperthyroidism presents a most difficult problem. Ocular signs may be those of sympathetic hyperactivity or orbital edema. If ocular protrusion is unilateral the diagnosis is even more difficult. The differential diagnosis includes all of the causes of proptosis and exophthalmos and may require a most searching history and examination. Particular attention should be directed to the possibility of the patient's having received one of the thiouracil salts without having special attention directed toward possible thyroid abnormality. Ocular conditions that must be excluded include carotid-cavernous fistulas, neoplasms and inflammations of the orbit, and myasthenia gravis. Carotid angiography and special orbital studies may be required to exclude local or neurologic disease.

In a small group of patients following medical or surgical correction of hyperthyroidism there is progression of the exophthalmos with the production of an edematous orbit. A number of different modes of treatment have been effective in preventing the exposure keratitis with the blindness that occurred several decades ago: systemic thyroid extract, transfrontal orbital decompression, early tarsorrhaphy, and hypophyseal radiation, each of which has a definite indication.

When extreme protrusion of keratitis threatens the eyes, a temporary type of tarsorrhaphy may be indicated. Usually, opposing denuded edges of the lids are sutured together and remain adherent. This type of procedure is not satisfactory for a permanent lateral blepharoplasty; a far more satisfactory procedure is that of Wheeler wherein the outer portion of the lids is split in the gray line, the lid margins are removed, and a tongue of lower lid is brought into a pocket of the upper lid.

Comment: Variability is the characteristic of endocrine exophthalmos. It varies in time of onset, in severity, in duration, and it may be unilateral or bilateral. It is a self-limiting disease, and is usually mild. Severe cases are relatively rare. These characteristics must be constantly borne in mind in evaluating any form of treatment and Dr. Newell has rightly emphasized this variability. It accounts for the breakdown of the classification of these ocular changes into two distinct groups. Although this division may be clinically convenient, it must not lull the physician into a false sense of security. Mild cases can become severe.

In the commentator's experience true glaucoma, and not simply an elevated tonometer reading, is no more common in medical exophthalmos than in the general population. In addition, despite recent electromyographic studies, there is no question, easily demonstrated at the time of surgery, that these eyes are held in depression by a tight inferior rectus muscle. The resulting failure of eyes to elevate during sleep together with the

lagophthalmos seems the most likely explanation for the development of exposure keratitis.

Dr. Newell has pointed out that hyperthyroidism associated with severe eye signs should be treated cautiously, for rigid control of the thyrotoxicosis may precipitate more severe eye changes. Therefore, any patient in whom the eye symptoms overshadow the systemic complaints should be treated cautiously.

ROBERT M. DAY

INTRAOCULAR PRESSURE

THE OCCURRENCE OF GLAUCOMA FOLLOWING OCCLUSION OF THE CENTRAL RETINAL ARTERY

A CLINICOPATHOLOGIC REPORT OF SIX NEW CASES WITH A REVIEW OF THE LITERATURE

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A. M. A. Arch. Ophth., 1959, *61:* 845–864

A clinicopathologic study of six cases of glaucoma after occlusion of the central retinal artery has been made. These cases together with a review of the literature led to the conclusion that glaucoma after occlusion of the central retinal artery is a distinct clinicopathologic entity, though a much less common one than glaucoma after occlusion of the central retinal vein. Typically there is an abrupt onset of ocular pain due to secondary glaucoma within nine weeks of the time of arterial occlusion. Treatment of this secondary glaucoma is generally unsuccessful, and the eye is frequently enucleated soon after the onset of ocular pain.

The pathogenesis of the glaucoma in these cases, like that which follows occlusion of the central retinal vein, is not understood. In the cases presented in this report there was clinical evidence that the ocular tension did not become elevated until after arterial occlusion. The frequency with which glaucoma follows occlusion of the central retinal artery is impossible to determine. It would appear that the condition is not nearly so rare as generally believed.

Histopathologic study in early cases before the formation of well developed anterior synechiae has provided evidence that something provokes an outgrowth of mesenchymal cells from the uveal tissues of the iris root. These cells invade the chamber angle to form a delicate membrane along the inner surface of the trabecula. It is this newly formed tissue which is believed to cause the initial obstruction to the outflow of aqueous. Subsequently, the formation of broad peripheral anterior synechiae aggravates the obstruction.

In four of the six cases of the present study, the eyes were enucleated before well developed peripheral anterior synechiae had formed. Each of these eyes revealed evidence of microhemorrhage in the anterior chamber angles. Each also revealed a proliferation of mesenchymal cells and minute blood vessels arising from the uveal tissues of the iris root and face of the ciliary body. Associated with this was the formation of an obstructing sheet of mesenchymal cells along the inner surface of the trabecula. Thus it would seem that the rise in intraocular pressure did not develop as a consequence of advanced peripheral anterior synechia but more likely as a result of the formation of a membrane covering the ordinarily large openings through which aqueous passes from the anterior chamber into the trabecula.

The diagnostic retinal changes which differentiate these cases from those of hemorrhagic glaucoma secondary to occlusion of the central retinal vein are as follows: There is widespread coagulative necrosis involving selectively the inner retinal layers. In those eyes enucleated early there is severe edema and great swelling of the nerve fiber layer, an incomplete disappearance of ganglion cells, a great reduction in cell population of the inner nuclear layer, and early degeneration and gliosis of the optic disk. Those eyes enucleated later may reveal profound shrinkage of the inner retinal layers, a complete disappearance of ganglion cells, and an excavated nerve head. There is no evidence of old or recent hemorrhage in the posterior segment.

Comment: After a series of recent reports of histopathologically verified cases of occlusions of the central retinal artery followed by secondary glaucoma, the authors' painstaking review of the 31 cases of this condition (including 6 of their own) recorded in the literature seems to tip the scale in favor of the tentatively expressed opinion that this is not such a rare occurrence after all.

This type of secondary glaucoma appears to be limited to the older age group, the youngest recorded age being 48, in contradistinction to that following occlusion of the central vein, which has been found as early as the third decade of life.

BERTHA A. KLIEN

LENS

THE ISOLATION, CRYSTALLIZATION AND PROPERTIES OF PROTEINS FROM RABBIT EYE LENS

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J. Biol. Chem., 1959, *234:* 329–334

From the publication by Mörner in 1894 until 1955 it was generally believed that the proteins of lens consisted of three chief components α-crystallin and β-crystallin the soluble proteins, and an insoluble protein component named albuminoid. Within the last 4 years immunological studies have suggested that there are five or six immunologically separate substances in the lens. The present study was performed to resolve this discrepancy.

Lenses from adult albino rabbits were decapsulated and homogenized with 0.9 per cent saline solution. After centrifugation the supernatant was decanted and extraction was repeated two more times. The combined extracts were diluted with distilled water to a concentration of 5 mg. of protein per ml. and run for 48 hours in the Spinco continuous flow electrophoresis apparatus. Analysis was made at 4°C. in Veronal buffer of pH 8.9 and ionic strength 0.02. The current was 60 ma. and the flow rate of the sample was approximately 3.2 ml. per hour. At the end of the experimental period, the paper was dried in an oven and stained with bromphenol blue and zinc sulfate in acetic acid. The fractions collected at the bottom of the curtain were dialyzed against distilled water and saved for further processing.

The stained curtain showed five separate components with different patterns of migration under the conditions of the experiment. Five peaks occurred in tubes numbered 7, 9, 12, 15 and 27. When extracts of lenses were made with 0.1 M sodium hydroxide, fractions 1 to 4 did not appear presumably because of destruction by alkali hydrolysis and only fraction 5 was identifiable.

By adding Veronal buffer to each dialyzed fraction and then adding saturated ammonium sulfate until the first faint cloudiness appeared, crystals could be obtained with fractions 1 to 4. Fraction 5 crystallized on standing in the cold for 1 hour. Crystals of buffer which appeared along with the protein could be removed by subsequent dialysis.

X-ray diffraction showed the presence of an organic compound which had a repetition pattern at 7.7 Å. Solubility tests showed that as the buffer salts were removed on dialysis, fractions 1 to 4 acted as euglobulins and precipitated out, whereas fraction 5 remained soluble.

Solubility in ammonium sulfate was determined by dissolving weighed amounts of salt in aliquots of each protein at pH 8.0. Solubility curves which had individ-

ual differences showed virtually complete precipitation at 50 per cent saturation with ammonium sulfate, once again indicating the presence of globulins.

Solubility determinations at varying pH's showed that fractions 1 to 4 had a similar isoelectric point lying between 5.0 and 5.5, whereas the isoelectric point of fraction 5 was at 4.6. The absorption spectrum of each substance showed a peak at 280 $m\mu$ corresponding to the content of aromatic groups.

Sedimentation values obtained in a Spinco analytical ultracentrifuge showed that fractions 1, 3 and 4 had identical sedimentation rates under the conditions of the experiment. Fraction 2 had the smallest value, and fraction 5 had an extremely large value. Fractions 1, 2, 3 and 5 were completely homogeneous in the ultracentrifuge, and fraction 4 had a slight trace of another protein which behaved like fraction 5. By assuming average values for the diffusion constant and the partial specific volume of each of the proteins, it was possible to estimate a molecular weight based upon sedimentation constants of other proteins. On this basis, the molecular weights of fractions 1, 3 and 4 lie in the range of 60,000 to 80,000 similar to that of serum albumin. The lower sedimentation rate of fraction 2 corresponds to a molecular weight of 15,000 to 25,000. Fraction 5 has a sedimentation rate which would place its molecular weight in the range of 1,000,000 to 1,500,000.

Comment: This report represents a notable milestone along the extending road of lens biochemistry. By using a relatively new technique plus some additional cautions in manipulation, the authors have given us five apparently pure crystalline components of the lens where not one pure substance had been isolated before. Whether study of these five substances gives direct new knowledge on the cataract problem is of no significance. It is only with such a meticulous approach that problems of chemical pathology in the eye field will eventually be solved.

ALBERT M. POTTS

CORNEA

LIPID KERATOPATHY AND ATHEROMA

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Circulation, 1958, *18:* 519–525

Lipid keratopathy as described in this paper consists clinically of a fatty plaque in an area of the cornea that has been previously vascularized. The multitude of names—dystrophia adiposa corneae, xanthomatosis, lipin interstitial keratitis, secondary steatosis among others—under which this condition has been described in the literature indicates the diversity of interpretations that have been attributed to the process. The purpose of this paper is to point out certain similarities in the fatty plaques of the cornea and blood vessels in man and in hypercholesteremic rabbits, and to suggest a common pathogenesis.

In the human cornea the fat appears usually in a fan-shaped distribution during the stage of neovasculogenesis in association with an active keratitis, or it may develop disk-shaped in the immediate area of the blood vessels in an otherwise white and quiet eye, years after the keratitis. It is usually reversible during an active keratitis and usually permanent and stationary when it occurs in a compact cornea. In a cornea that has been diffusely vascularized the distribution of the fat is that of a diffuse inundation rather than plaque-like.

Histologically, the fatty plaques of the human cornea contain two types of sudanophilic lipid: (1) globular lipid in the form of bright red droplets, often as large as 20 μ in diameter, situated predominantly within the cells and abundant in proportion to the cellularity of the tissue, (2) granular lipid, *i.e.*, sudanophilic granules situated predominantly in the acellular and hyalinized areas. The granular type is usually sparse or absent from areas of globular sudanophilia, but the reverse is not so true. The impression is that the former is derived from the latter when the cells containing the globular lipid disintegrate.

With hematoxylin and eosin stains, the cornea with lipid keratopathy shows an increase in cellularity in some areas and a decrease of cells in others. Frozen sections examined with Polaroids often show abundant birefringent crystals, especially in areas of hyalinization.

Fatty plaques similar to these, except that there was less necrosis and correspondingly less sudanophilia, were induced in about 12 hypercholesteremic rabbits whose corneas were vascularized. If vascularization was induced before the animals were put on a high-cholesterol diet for periods of 6 to 12 months, lipid was deposited to some extent in the paravascular regions, but if a localized vas-

cularization was induced while the animal was hypercholesteremic, a dense lipid plaque developed in the area of the blood vessels.

The fatty plaques found in the blood vessels of the rabbits show changes that are practically identical with those of human atheromata. In both cases the plaques tend to localize about orifices of blood vessels. They consist of hyperplastic intima loaded with sudanophilic material and birefringent crystals. These have the same distribution as in human atheromata, that is, intracellular globular lipid adjacent to the lumen and media with extracellular granular lipid in the intermediate necrotic areas. The mutual exclusiveness of the two types of lipid is often striking in the rabbit atheroma. The birefringent crystals are associated with the areas of necrosis and can be seen by ordinary light microscopy.

The chief basis for identifying the fatty plaques of the cornea and those of the blood vessels is the similarity in their histologic features. Common to both are the intracellular globular lipid associated with active hyperplasia of tissue, and the extracellular granular lipid associated with hyalinization and necrosis of tissue. In both there tends to be a mutual exclusiveness of the two types, and one appears to be converted into the other with necrosis of the tissue, in the direction of globular to granular sudanophilia. Associated with this is a release of birefringent crystals that appear to be, in part at least, cholesterol.

Although small differences in the fatty plaques of the human cornea and that of the hypercholesteremic rabbit are recognized, in both cases what is happening in the cornea appears similar to what is happening in the blood vessels of the corresponding species. If the pathogenesis and course of events for lipid keratopathy and atheroma are identical, as suggested by these histologic findings, one would expect atheroma to develop only in areas of prior vascularization and with episodic suddenness. Both these possibilities have been suggested on other grounds, but it has not heretofore been recognized that the cornea may provide an informative analog for the visualization of the atheromatous process during life.

The possibility that persons with this type of lipid keratopathy are prone to atheromatosis or *vice versa* cannot be answered on the basis of the present cases since no autopsies were done on the patients with corneal plaques.

Of the 10 patients on whom blood cholesterol determinations were made, the average level was 267 mg. per 100 ml. It thus appears that lipid plaques occur in the cornea, as they do in blood vessels, predominantly but not exclusively in patients with higher than average blood cholesterol levels.

Comment: The subject of this paper is not only fascinating because it is concerned with a condition which has been given various clinical interpretations but also because it suggests characteristics of the cornea which have as yet hardly been touched upon. One of these is the occurrence of so-called clearing lines or clear lines which are probably related to the ray-like distribution of certain lipid deposits mentioned in this paper and to other more irregular deposits. In this reviewer's experience these clearing lines appear to be present in early lipid deposits and are simply areas where lipid is absent. Probably it is related to anatomic channels in the cornea which our methods of sectioning have not yet permitted to be elucidated. That such is the case is suggested by observations in elderly

patients with arcus senilis distributed in anterior and posterior sheets in the corneal periphery for 2 or 3 mm. These sheets show clear lines which form a network suggesting the outlines of crocodile skin. This suggests the lipoid nature of so-called crocodile shagreens, both anterior and posterior.

Another observation which may be of value to those interested in this subject is that ointments applied to corneas in patients who have permanent intermarginal sutures for relief of exposure keratitis develop lipid deposits which assume the shape of the interpalpebral fissure. The lipid component of these ointments apparently penetrates especially well through the exposed epithelium which is drier than normal anyway.

This paper suggests that much thought be given to the still unanswered questions of ingested cholesterol and lipoid deposits and the chemical changes associated with conversion of globular to granular sudanophilia.

SAUL SUGAR

DELAYED MUSTARD GAS KERATITIS: A REPORT OF FIVE CASES TREATED BY LAMELLAR KERATOPLASTY

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M. J. Australia, 1959, *46:* 529–530

Following the 1914–1918 war, men discharged without eye disability later developed mustard gas keratitis. By 1947, 243 cases had been reported. Characteristically the history shows a long period free from disease, followed by repeated ulceration and fluctuating deterioration of vision, the exacerbations accompanied by photophobia, lachrymation, and pain. At the intrapalpebral fissure adjacent to the limbus, white ischemic areas are surrounded by dilated veins, and the rest of the conjunctiva is conjected. Ulcers follow no regular pattern. Scholz and Woods discuss as possible causes tissue sensitivity, destruction of mucus glands, corneal anesthesia, vascular abnormalities, cholesterol crystals, and loosening of corneal epithelium.

Treatment has been symptomatic, including padding the eye, atropine, antibiotics, tarsorrhaphy, and contact lenses; at times enucleation has been necessary. The possibility of keratoplasty has been mentioned, and Macindoes relieved pain in one case by this operation. Most have hesitated to perform corneal grafts in these cases since the operation is technically difficult because of the irregular thickness of the cornea and because the patient cannot be promised improved vision. However, five old cases were operated upon because of the probability of relieving pain. In all cases vision has been improved and symptoms relieved; the morale of the patients improved noticeably.

Comment: The author reviews the literature and gives the clinical pattern for delayed mustard gas keratitis. Five cases are reported which were treated by lamellar keratoplasty. All of these cases resulted in relief of ocular symptoms with visual improvement.

Even though the number of patients now seen with this specific type of corneal disorder is few, the author emphasizes another indication for therapeutic corneal grafts.

ROBERT D. MULBERGER

CORNEAL HOMOGRAFTS AND HETEROGRAFTS PRACTICED WITH TRANSPLANT MATERIAL PRESERVED BY LYOPHILIZATION

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Ann. ocul., 1958, *191:* 636–669

Lyophilization is a process of preservation which combines rapid freezing and dehydration of the frozen product under high vacuum. This definition accepts the possibility of rehydration. Many methods of lyophilization are possible, and this explains the considerable differences in the results achieved by research and experimentation. If we wish to assure for the rehydrated tissue a structure analogous to its original one, a certain number of precautions are necessary, in the processes of freezing, dehydration and also rehydration.

In order to avoid destruction of the tissue, freezing must be very rapid, instantly achieving a temperature below −40°C. For this purpose the specimen must be thin; the surfaces must adhere immediately and directly to the refrigerating medium. If the source of freezing is solid (carbonic ice), the use of a dampening intermediary in which the specimen must bathe directly is indispensable. If the source of freezing is liquid, for instance liquid propane, the results will be satisfactory only if this liquid dampens the specimen completely. Liquid nitrogen is much less satisfactory. The preceding operations may be carried out after the tissue has been impregnated with a protective solution of physiologic liquid, with 30 per cent glycerol added. This will increase the safety of the freezing process but the dehydration concentrates the glycerol in the tissues in a possibly damaging manner.

The human eyeballs are taken from the cadaver in the usual way; from animals they are enucleated immediately after death. Although the authors are obliged to preserve them for a maximum period of 24 hours in a humid atmosphere of +4°C. immediate preparation after enucleation would be desirable. They are emptied aseptically, mounted on special supports extending the sclera so that it preserves its regular shape and is immediately lyophilized. Then they are abruptly dumped into a mixture of alcohol at 90°C. and carbonic ice, −79°C. After

5 minutes they are bottled; the openings of the flasks are covered by a filter. Then dehydration is carried out at a temperature of approximately −50°C. for several hours under high vacuum. Reheating of the flasks must be very gradual and carefully supervised when dehydration has been completed. This is usually carried out within 18 to 20 hours. The flasks are then hermetically closed in a nitrogen atmosphere which is subsequently rarefied. They are then ready for indefinite preservation and may be sent out over great distances without special precautions.

The grafts present dead tissue but the histologic structure is preserved and its antigenic character is diminished. At the time of use, rehydration is carried out by aseptic filling of the flask with lukewarm physiologic serum at +35°C. This rehydration takes about ½ to 1 hour for the eyes of rabbits or dogs and 1 to 1½ hours for human eyes. The eyeballs resume their consistency and the corneas their transparency to a considerable degree. Then they are rinsed thoroughly in fresh physiologic serum so that certain antigenic substances liberated by lyophilization are removed. Histologic observation has shown that, in case the freezing process has been very rapid, after an hour of rehydration Bowman's and Descemet's membranes are approximately intact. The stroma seems reasonably normal, with a very slight degree of lamellar dissociation.

The authors' experimentation extends over 119 cases of different corneal grafts, including 29 human cases. The results established that with such grafts the lamellar homotransplants were equal to those practiced with fresh corneal grafts. The penetrating homotransplants seemed to give good results but that point needs further clinical experimentation. Lamellar heterotransplants were made with durable success—several months in human cases—on the condition that donor material was carefully selected. The penetrating heterotransplants were always a failure.

The grafts consist of dead tissue, but after rehydration they return to an almost normal physical and histologic structure. They have partially lost their antigenic character; bacteriologically they are sterile. From the clinical point of view we may summarize that these prepared grafts allow the use of lamellar homografts with results comparable in every respect to those obtained by fresh grafts. Penetrating homografts always take and good results are possible, but experience in man is still limited. Lamellar lyophilized heterografts have shown good and durable results in man with the use of the dog as donor. The cornea of the pig, on the other hand, proves to be unsuitable material. Other types of donors will have to be investigated. The results with penetrating heterotransplants in animals have been invariably negative.

These lyophilized grafts in man perform almost like fresh grafts. As a rule they are transparent from the beginning and are usually surrounded by a limiting ring. In animals, on the other hand, the graft usually clears after a few weeks, without leaving an opaque zone. The action of these homoplastic as well as heteroplastic grafts is architectonic, optic, trophic (remarkably so even in heterografts) and therapeutic (especially in herpes). These effects were observed during several months; once they appear, they are usually permanent.

Reactions of incompatibility appear in two ways: In the first type, the reactions are early, according to the general rules for tissue incompatibility. This is the case in penetrating heterografts, and the clinical case of a heterograft from a pig, where the transplant was rejected on the 25th day. Those were doubtless antigenic reactions. In the second type, which was observed in man, and only observed twice, late incidents occurred: temporary hypertonia of the eyeball with opacification of the graft in the 3rd month, or fine vascularization with partial opacification of the graft in the 5th month. It is the authors' opinion that these are diseases of the graft, analogous to those observed in fresh homografts, of unexplained pathogenesis as well.

It may be stated in conclusion that the process of lyophilization tends to bring the heterograft closer to the homograft. In both cases the graft acts only through the conjunctival skeleton which it offers for rehabitation by the host cells.

The problem is, of course, far from exhaustively solved. The results offered here lead, in the contrary, to new problems, especially in their anatomopathologic and biologic aspects, which merit further study.

Comment: This experimental study of 119 cases of different corneal grafts, which includes 29 human cases, is undoubtedly another contribution to the necessary research required before the results of corneal graft surgery can be adequately predicted.

The authors' method of freezing, dehydration, and rehydration is described. Apparently, their results with the use of lamellar homografts preserved by lyophilization is favorable and comparable with the reported results of others. Their reports on the use of lamellar heterografts, although more encouraging than in cases of penetrating heterografts, still require further experimental, anatomic, biologic, physiologic, pathologic and clinical study.

It is agreed that in this study, the process of lyophilization may bring the heterograft closer to the homograft. This report should become a part of the literature on corneal grafts.

ROBERT D. MULBERGER

NEOPLASTIC DISEASE

WHY DO CANCER PATIENTS DIE?

J. D. HARDY

Jackson, Mississippi

Surg., Gynec. & Obst., 1959, *108:* 368–369

The author points out that venous blood draining tumor areas and peripheral blood frequently reveal cancer cells. It must be assumed, therefore, that embolic cancer cells are frequently implanted distally over the body and that some forces hold these cells dormant for a very long time, or inhibit their growth completely. The forces are probably immunological in nature and when the implanted cells do take on active growth it is because the aggressive biological activity of the tumor breaks through the immunity of the host. The author points out that tumors do produce demonstrable biochemical lesions, perhaps at an enzymic and, ultimately, a molecular level. Thus, surgical thought has been extended to embrace the concept of cancer as a systemic or biochemical disease radiating initially from a single focus and later maybe from metastases. Thus cancer can be viewed as a metabolic aggressor. The cause of death in the presence of far-advanced cancer is an extensive derangement of normal biochemical functions and in this respect the similarity between malignant disease and sepsis is once again emphasized.

Comment: Sections of eyes with malignant melanoma of the uvea frequently show a mass of cancer cells in the lumina of the blood channels of the tumor. It is an inescapable fact that cancer cells are usually implanted distally over the body.

Engle (Cancer cells in the circulating blood. Acta chir. scandinav., Suppl. 201, 1955) found tumor cells in the venous blood draining tumor areas in 75 of 123 various types of malignancy. Tumor cells were also found in the peripheral blood in 10 of 79 patients with operable malignancy and in 7 of 14 patients with inoperable malignancy. Roberts *et al.* (Technique and results of isolation of cancer cells from circulating blood. A. M. A. Arch. Surg., *76:* 334–346, 1958,) found cancer cells in 12 of 72 "curable" patients, in 9 of 28 "incurable" patients, and in none of 14 controls. Also, in 12 of 62 patients he and his co-workers demonstrated cancer cells during surgical manipulation, 5 of which had been negative before surgery. Also, 2 patients with positive counts were negative for cancer cells following surgery. In another report, Roberts *et al.* (The response of cancer cells in the circulating blood to surgical stress and chemotherapy, Surg. Forum, *9:* 595, 1958) found a drop in cancer cell count in the peripheral blood during treatment with nitrogen mustard and Thio-TEPA. The effect of different modalities has been compared by this method.

This exciting new work which confirms previous surmises indicates that it is not a question of whether cancer cells metastasize to distal sites but a question of whether or not they are able to survive and grow at these sites. This poses many important questions such as the role that the primary site has in the immunological process and whether or not in some stages and in some tumors the primary site does not favor immunity. Do

these new findings negate the principle of block dissection? Can the resisting forces be better understood so that they can be stimulated as they are against bacteria?

It might be added that the technique for demonstrating cancer cells in the peripheral blood, as described by Roberts *et al.*, is a relatively simple one whereby the erythrocytes are eliminated by sedimentation and the leukocytes by centrifugation. The cancer cells are then detected by the Papanicolaou technique.

A. B. Reese

THE BASAL-CELL NEVUS

Its Relationship to Multiple Cutaneous Cancers and Associated Anomalies of Development

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A. M. A. Arch. Dermat. & Syph., 1959, *79:* 67–80

The authors present four cases illustrating the various clinical features and therapeutic problems encountered in patients with basal-cell nevi. The basal-cell nevus is a dysgenetic dermatosis characterized by multiple small cutaneous tumors. These are histologically indistinguishable from basal-cell cancer. Malignant supervention is common, generally resulting in multiple basal-cell cancers of the face in young adults. Developmental defects of other systems are often present. Incidence seems to be based on an inherited, sometimes familial, predisposition.

Basal-cell nevi may appear at birth or be first noted in infancy. Occasionally the lesions may begin at about puberty and gradually increase in number and in size over a period of years. There may be few or hundreds, and there is a tendency towards bilateral but not necessarily symmetrical distribution. The size of the individual lesion varies from that of a pinhead to about 5 mm. in diameter. Pedunculated and papular lesions are common on the neck, eyelids and axillae.

Frequent associated anomalies of development include multiple dental follicular cysts of the mandible or the maxilla, bifurcation of one or several ribs, milium-like bodies on the face, and epithelial cysts of the skin. Other defects of development are lipoma, fibroma of the ovary, congenital dorsal scoliosis, agenesis of the corpus callosum, and sometimes feeble-mindedness. These anomalies may represent a familial trait, and in each case the patient's pedigree should be thoroughly investigated.

The presenting complaints in patients with this syndrome may be caused by the cysts of the jaw or maxilla, although occasionally enlargement of a cutaneous

lesion or its ulceration will cause the patient to seek medical attention. An important feature of the syndrome is the occurrence in young adults of multiple skin cancers developing from, or associated with, the basal-cell nevi. Treatment in general may be both prophylactic and definitive. Prophylactic treatment of the nevi as a means of preventing cancer is highly desirable, especially in the region of the eyelids and nose. All basal-cell nevi on these areas should be removed or completely, yet conservatively, destroyed. This may be accomplished adequately by cautery, electrosurgery, excision or freezing with liquid oxygen or nitrogen. In some instances there are so many lesions that removal of all of the basal-cell nevi would not be practical. Frequent examination may be needed to detect early malignant change in any lesion.

A single basal-cell cancer resulting from a basal-cell nevus can be treated by any of the conventional means. The problem cases are those in which the patients present multiple rodent ulcers about the nose or eyelids. In these, surgical methods, including chemosurgery, should be used in preference to irradiation, since the rodent ulcers are multiple and new cancers may be expected to develop over a period of many years. The use of irradiation would be unwise because of the large areas of roentgen dermatitis that might result. In far-advanced lesions, the problem of therapy may be formidable, and it may require consultation and cooperation between the ophthalmologist, surgeon, radiation therapist, and dermatologist.

Comment: This lesion is essentially a multiple congenital basal-cell carcinoma—one of the newer variants of this condition. As the lesion does not contain "nerve cells" this term seems histologically to be confusing.

Inasmuch as the tumors occur commonly in the eyelids and as early treatment is essential, recognition of this lesion by the opthalmologist is important.

T. S. SANDERS

Comment: The authors describe a rare and generally unappreciated condition in which ophthalmology has a stake. These multiple, congenital, and usually benign basal-cell epitheliomas or basal-cell nevi may become true basal-cell carcinomas and this is particularly true when they involve the lids and caruncle. They have a familial tendency and may be associated with developmental aberrations, particularly cysts of the mandible or maxilla.

A. B. REESE

DIAGNOSTIC TECHNIQUES

OPHTHALMODYNAMOMETRY

ROBERT MONES

J. Mt. Sinai Hosp., 1959, *26:* 71–77

Retinal veins have long been known to palpate in normal persons, but the arteries do not do so unless the globe is compressed. In 1917 Baillart described an instrument, the ODMeter, by means of which the tension of the compressed eye could be measured so that for the first time the tension at which the retinal artery begins to pulsate could be determined. This study evaluates ophthalmodynamometry as a tool in clinical neurology.

The flat part of the instrument is placed against the lateral aspect of the globe and pressure is slowly exerted. When the arteries begin to pulsate, the pressure is read; the reading corresponds to diastolic pressure. Further pressure against the eyeball leads first to increase, then to decrease, in pulsation, and finally to entire cessation of pulsation, sometimes accompanied by transient blindness. Reading at this point corresponds with systolic pressure. Normal intraocular pressure is about 20 mm. Hg, and diastolic retinal artery pressure about 60 mm. Hg in patients with normal systemic blood pressure. Retinal vein pressure is usually a little higher than intraocular pressure and therefore higher than systemic vein pressure. Absolute recordings are written exactly as are diastolic-systolic systemic blood pressure readings. The examination is rapidly and easily done, though about 20 per cent require local anesthesia and the method cannot be used unless the fundus is clearly visible. It is contraindicated in glaucoma, retinal artery thrombosis, chorioiditis, high myopia, or any condition predisposing to retinal detachment.

For neurologic examination, the absolute diastolic-systolic reading is unimportant, but differences between pressure in the two eyes not accounted for by eye conditions, or changes in pressure in one eye before and after medical or surgical treatment may be significant. Forty patients with papilledema, aneurysms, optic neuritis, brain tumors, or vascular disease were studied. Striking changes in both eyes were not noted in this series, and the diastolic—but not the systolic—readings correlated with the clinical picture. Of seven cases with demonstrated narrowing of the coronary artery on one side accompanied by neurologic symptoms, six had systolic arterial readings 20 per cent or more lower in the ipsilateral eye; in one case the reading was only 15 per cent lower. One patient studied before and after carotid artery ligation showed a 50 per cent change after the procedure.

Our study corroborates observations of others indicating that: (1) differences in ODMeter readings between the two eyes show a defect in blood supply in the eye with the lower tension, (2) about 80 per cent of patients with carotid artery disease have significantly lower readings in the ipsilateral eye, (3) surgical occlusion of the common or internal carotid causes significant drop in the ipsilateral retinal artery pressure reading, (4) surgical endarterectomy can reverse

abnormal readings and can be corroborated by angiograms, (5) tumors invading the carotid area have produced similarly lowered readings, and (6) false readings are rare.

Since carotid artery disease appears to be commoner than was thought and can be well treated, and since other methods of diagnosis are not entirely satisfactory, ODMetry proves valuable as a simple method for routine use.

Comment: Balliart's invention of the ophthalmodynamometer in 1917 provided a rapid, practical method for measurement of the retinal arterial pressure. Numerous enthusiastic observations were made of these pressures, and the results extrapolated to clinical conditions of wide scope. In 1926 Duke-Elder dampened the enthusiasm for the clinical usefulness of ophthalmodynamometry by stating, "the unwieldy literature that has accumulated upon the subject is swollen with wearisomely protracted . . . discussions of unnecessary hypotheses, with defective and confused experiments . . . with a multitude of theorizing and a paucity of facts."

However, in the past 6 years practical therapy in occlusion of the carotid arteries has prompted re-appraisal of the value of ophthalmodynamometry. The present paper is a clinical study by a neurologist of the value of this technique in the diagnosis and management of occlusion of the carotid artery.

Ophthalmodynamometry was performed on 40 patients with papilledema, aneurysms, optic neuritis, brain tumors, and central nervous system vascular disease. Of these patients, 33 had no significant difference between the two eyes and no clinical or angiographic evidence of occlusive disease of the carotid artery. The author found 7 cases of spontaneous narrowing or occlusion of the carotid artery, proved by angiography. Out of these 7 cases, 6 showed lower measurements in both the systolic and diastolic retinal artery pressures in the ipsilateral eye. In positive cases the systolic retinal artery pressures differed 20 to 60 per cent on the ipsilateral side. This is in agreement with the figure of 20 per cent difference in systolic retinal artery pressure currently reported throughout the country.

The author concludes that the systolic is the most important pressure measurement and supports this by citing the study by Bakay and Sweet in which direct pressure measurements of the distal carotid artery were made under surgical exposure. They found that the diastolic retinal artery pressure was near normal after carotid ligation or occlusion, whereas the systolic retinal artery pressure was significantly lower than the systemic systolic blood pressure. J. L. Smith *et al.*, in a recent study of 6 cases of occlusive carotid disease, support the author by finding that the systolic retinal artery pressure was more apt to be unequal while the diastolic pressures were approximately the same. Mones concludes that a systolic difference in retinal artery pressure of over 20 per cent indicates ipsilateral arterial insufficiency, and 80 per cent of patients with carotid occlusive disease will show this systolic retinal artery pressure difference. I agree and think that enough evidence has been compiled so that the figures of greater than 20 per cent difference in systolic retinal artery pressure and greater than 15 per cent difference in diastolic retinal artery pressure can be considered abnormal and indicative of occlusive disease of the carotid arterial system.

In our age of medical abbreviation (in which all of us are guilty), I feel that the author made an unfortunate choice in abbreviating the ophthalmodynamometer "the ODMeter", and ophthalmodynamometry "ODMetry". While admittedly the Greek roots are a mouthy derivation, one feels that "ODMeter" only adds to the bewildering morass of obfuscating capital letters already present in the medical literature.

JOSEPH AMDUR

Basic Sciences

MICROBIOLOGY

THE BACTERIAL FLORA IN TRACHOMATOUS AND NORMAL CONJUNCTIVA

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Rev. Internat. Trachome, 1958, *4:* 361–370

An investigation on the influence of bacterial contamination on the mode of onset of trachoma appeared desirable since in the opinion of many ophthalmologists the acute onset of trachoma usually depends on bacterial superinfection. Some Japanese schools postulate the acute or sudden onset. Research was carried out at nine places in Okayama Prefecture, located in the southwest of the main island of Japan. The incidence of trachoma in these nine places was 12 per cent to 56 per cent, average 29 per cent including trachoma dubium.

For this study 247 cultures (trachoma 150, trachoma dubium 51, normal 46) were made on 7,099 people of the area. Positive growth of culture was obtained in 88 to 94 per cent of each group. Among 14 kinds of microorganisms, the one most frequently demonstrated was staphylococcus and corynebacterium xerose followed next. In kind and frequency of microorganism, no special correlation was found among trachoma, trachoma dubium, and the normal group. According to the results of hemolytic and coagulase tests, pathogenic staphylococcus was not demonstrated in increased percentage from trachomatous eyes. There seems to be little significance in the distribution of microorganisms as causative agents of conjunctival inflammation. Of 35 strains of staphylococcus isolated from trachoma patients 11.4 per cent were positive in the coagulase test. There seems to be no significant difference between the pathogenicity of staphylococcus isolated from trachoma patients and that from normal eyes.

In the experimental treatment designated to remove the contaminated microorganisms with streptomycin and polymyxin, these contaminating microorganisms were not found to influence the manifestations of trachoma to any significant extent. Twice daily the combined polymyxin-streptomycin ointment was given in 19 cases of trachoma, for a period of 2 months. Bacteriological examinations were made before the treatment and 10, 30 and 60 days after the treatment.

The incidence of microorganisms was around 90 per cent in trachoma, in tra-

choma dubium and in the normal group, and there was no evidence that the incidence of contamination in trachomatous eyes was greater than in the others. The kind of microorganisms isolated from each group showed no specificity and there was no tendency of infection by certain bacteria in trachomatous eyes. From a statistical viewpoint, in Japan, especially in the district under study, bacterial conjunctivitis did not so frequently influence the trachoma symptoms as has been reported from Egypt and Tunis.

The influence of contaminating microorganisms in trachomatous eyes was determined in several ways; it was found that most of the contaminating microorganisms in those eyes were nonpathogenic and had little influence upon the manifestations of trachoma. It seemed to be relatively rare that the existence of bacteria in the eyes produced additional inflammation or prolongation of the course of the disease. These conclusions do not exclude the evidence that superinfecting bacteria produce an additional inflammation in some trachomatous eyes.

Comment: It is of interest that in Japan the bacterial flora of normal and trachomatous conjunctivas show no significant differences, and that the course of clinical trachoma there is apparently unaffected by ordinary bacterial superinfection. Recent reports from Saudi Arabia and Portugal indicate the existence of a similar situation in these areas.

No isolation of *Neisseria gonorrhoeae* is reported in this series. There are reports that gonorrheal superinfection can markedly aggravate existing trachoma.

For practical purposes, adequate antitrachoma therapy with topical tetracycline and systemic Gantrisin (Thygeson, Trachoma Manual and Atlas, U. S. Public Health Service Publication No. 541) should be effective against the majority of contaminating bacteria as well as against the elementary bodies of trachoma.

HENRY F. ALLEN

SIGNIFICATO E LIMITI DELLA RICERCA DEL TEST DELLA PROTEINA C REATTIVA (PCR) IN OFTALMOLOGIA

(SIGNIFICANCE AND LIMITS OF RESEARCH ON THE C-REACTIVE PROTEIN TEST (CRP) IN OPHTHALMOLOGY)

G. ALAGNA

Eye Clinic of the University of Messina, Italy

Boll. ocul., 1958, *37:* 929–948

Since the isolation of the C-reactive protein (CRP) by Tillet and Francis in 1930 from the blood serum of a patient with pneumococcic pulmonitis, numerous studies on the nature of CRP and its presence in the serum of patients with a variety of diseases have been published. Only a few, however, pertain to ocular

conditions. The present study is the first published in the Italian ophthalmologic literature.

The subjects were 114 patients of both sexes and ranging in age from 7 to 73 years, seen at the University of Messina eye clinic. For the CRP determinations the patient's serum was mixed with CRP antiserum in a capillary tube and kept in the incubator at 37°C. for at least 12 hours. Sedimentation rates were determined by Westergren's method for comparison. The correlation between the two tests in the entire series was 80 per cent.

Both tests were carried out at the time of first examination and in those with positive reactions, also at the end of treatment (or after the operation) when cure or at least amelioration of the initial disease had been obtained.

Three- or four-plus reactions were found only in conditions in which inflammatory or necrotic suppurative features predominated, such as abscess, erysipelas, phlegmon or epithelioma of the eyelids, diphtheritic conjunctivitis, iritis and iridocyclitis of various kinds, central serous retinopathy, acute chronic and hemorrhagic irritative glaucoma, uveitis and episcleritis, and Reiter's syndrome. All the cases in which a rheumatic background was present or suspected were in this group.

Two-plus reactions were observed in trachoma with corneal complications, parenchymatous keratitis, tuberculous iridocyclitis, luetic iritis and chorioiditis, hypertensive retinopathy, albumineric neuroretinitis, thrombosis of the central retinal vein and retrobulbar neuritis.

One-plus reactions were obtained in cases of ulcerous blepharitis, acute catarral conjunctivitis, trachoma, simple chronic glaucoma, luetic iritis, tuberculous iridocyclitis, chronic mucopurulent dacriocystitis and other conditions.

The patients lacking CRP included, among others, subacute and angular conjunctivitis, chronic mucopurulent dacriocystitis, keratitis of various types, senile cataract, simple chronic glaucoma, luetic sclerochoroiditis, and retinitis pigmentosa.

It is concluded that CRP is not specific for the diagnosis of disease but it does provide an index of the "activity of disease" with respect to the severity, course and outcome.

Of particular interest are the examples furnished by the four patients with episcleritis, one with perforating scleromalacia, six with iritis, one with uveitis relapsing to hypopion, one with Reiter's syndrome, one with Chauffard-Still disease, one with central serous retinopathy, one with intrabulbar optic neuritis and one with paresis of the internal rete, where four-plus reactions were obtained initially and became negative when the ocular condition was resolved.

Comment: This exhaustive paper on C-reactive protein in ophthalmic pathology throws some additional light on the role this sensitive test might play in diagnosis, and, above all, in evaluating the therapeutic response of a given condition.

The first part of the paper is devoted to an extensive review of the literature concerned with CRP. In mentioning the paucity of CRP studies in ophthalmic literature, the author quotes the first series published by Wolkowicz *et al.* (Am. J. Ophth., *41:* 942, 1956) where the CRP test was evaluated and compared with a large series of controls. Doctor Alagna

is apparently not familiar with the later work of the same authors (A. M. A. Arch. Ophth., *59:* 389, 1958) on experimental uveitis where the behavior of CxRP was studied in rabbit aqueous.

The second part of the paper analyzes the clinical material consisting of 114 patients, their ages ranging from 7 to 73. These patients represent presumably a cross section of ocular pathology as seen in the eye clinic of the University of Messina. All these patients had a CRP test and sedimentation rate done at the onset of the disease and upon the completion of treatment. CRP testing was done by the same method as practiced in our laboratories: the suspected serum was mixed with CRP antiserum in a capillary tube and kept in the incubator for 12 hours. The sedimentation rate was done by the Westergren method. It is logical to compare these two tests in a given condition as both are positive under similar circumstances. Sedimentation rate reflects a shift in the serum protein ratio whereas CRP is a new serum protein attached to the α-globulin preceding the appearance of antibodies in the blood stream.

Unfortunately it is difficult to draw any valid conclusions from a series of ocular conditions ranging from a chalazion to retinal detachment and including about everything in ocular pathology a busy eye clinic has to offer. While the enclosed tables support the point the author intended to prove, namely, the parallel sensitivity of the CRP and sedimentation rate tests in those ocular conditions where a rheumatic background is suspected, the results obtained in the different pathologic groupings can be greatly misleading. For instance the statement that out of 2 cases of a hordeolum, 1 had a positive CRP test. Since no systemic survey is mentioned (which could well reveal the cause of a positive CRP test), the reader could get the impression that a stye is capable of making CRP appear in the blood stream. A similar objection could be raised to positive CRP results in central serous retinopathy "secondary to rheumatoid arthritis", convergent strabismus, following influenza, senile cataract "secondary to rheumatoid arthritis" to mention only a few. I am sure the positive CRP test reflects the systemic condition where the ocular "complications" had very little influence on the appearance of CRP in the blood stream. Those cases, therefore, represent systemic, and not ocular diseases where the ocular condition is coincidental and as such could well be omitted for the sake of clarity. Some results bring up an interesting point but they must be cautiously interpreted because of lack of controls or small number of cases. An example in point is epithelioma of the lid; both cases included in the tables had strongly positive CRP tests. An analysis of a large series with adequate controls would prove very useful, since positive CRP tests in malignancies where tissue necrosis occurs were reported. Here a positive result in a case where the diagnosis is uncertain could obviate the necessity of a biopsy. Presence of CRP in active trachoma is another interesting observation. Again, a larger, better documented series will be needed to draw any valid conclusions.

This commentator was particularly interested in the results obtained in uveitis since in our most recent series of 87 cases CRP and sedimentation rate were done simultaneously. I was able to single out from Doctor Alagna's tables 14 cases of uveitis which, judging from the description, would be classified as "nongranulomatous" and 8 cases fitting the description of "granulomatous". CRP test was positive in all 14 cases of "nongranulomatous uveitis". This is at variance with our statistics where 34.5 per cent had a positive test. If one assumes that those cases were not selected but tabulated in "order of their appearance" in the University Clinic, then the American reader will find the etiologic diagnosis quite at variance with the one he habitually encounters in our eye services. Out of 14 cases 9 had the etiologic diagnosis given as rheumatic or rheumatoid arthritis. Four cases were diagnosed as having a rheumatic fever background. This differs greatly

from our experience. Since the work of Woods on the role of streptococcus in uveitis was published it was always puzzling how infrequently one can incriminate rheumatic fever in the etiology of uveitis, in spite of the fact that the part played by the streptococcus in this disease is beyond any doubt. Three cases were secondary to tuberculosis and two to lues. One can surmise that the etiology of such polymorphous condition as uveitis can present a different etiologic background from one country to another. While I have no statistical data to support this statement, I think that there is a general agreement among students of uveitis in this country that 75 per cent of all cases of uveitis present an unknown or uncertain etiology. It also makes one wonder how little progress has been made in pinning down this elusive disease called uveitis as to its causative agent. Among 8 cases of "granulomatous uveitis" 3 had a positive CRP test. This compares favorably with 24 per cent of positive results in our cases.

The over-all correlation between CRP test and sedimentation rate in this series is 80 per cent. A similar correlation appeared in our series, although, our cases were more selective: 77 per cent in the nongranulomatous and 69 per cent in the granulomatous group.

The author's conclusions that CRP is not a specific biological test for diagnosis of ocular disease is in agreement with our observations. In fact in our experience the CRP test was not discriminating enough to help classify a case of uveitis into granulomatous and nongranulomatous. I am also in agreement with the author that the test, by virtue of its early appearance and faithful reflection of the progress of ocular disease, when rheumatoid arthritis is in the background, has its place in our diagnostic and therapeutic armamentarium.

MICHEAL WOLKOWITZ

CLINICAL SIGNIFICANCE OF THE RHEUMATOID SERUM FACTOR

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WITH THE ASSISTANCE OF FRIDA BIER

Rheumatism Research Centre, University of Manchester and Manchester Royal Infirmary

Brit. M. J., 1959, *i:* 523–530

Since 1949 the rheumatoid serum factor has been estimated by the sheep cell agglutination test (SCAT) routinely for all patients admitted to the rheumatoid beds of the Manchester Royal Infirmary and from selected groups of outpatients. The results of these tests, as well as those obtained on sera collected during surveys of both random and screened samples of the general population are presented in this paper. Titers recorded after 18-hour incubation were used throughout the analyses as experience has shown that these are more closely related to the clinical findings. In analyzing the material the results obtained at the first test in each case were used since not all the cases were serially tested.

A positive result in the SCAT was found in 93 per cent of 382 in-patients in whom the diagnosis of rheumatoid arthritis had been established on the basis of x-ray films of the joints and laboratory tests such as E.S.R., blood count serum uric acid and L.E. cells. Of these, 192 had subcutaneous nodules, and 98 per cent of these 192, had positive tests. Positive tests were obtained in 70 per cent of 64 patients with rheumatoid arthritis of less than 1-year duration and in 68 per cent of 41 patients with rheumatoid arthritis in whom an alternative diagnosis was recorded at some stage of their care in the hospital. In these two groups the diagnosis was less certain, and this is reflected in the lower proportion of positive tests.

Seventeen (41 per cent) of 41 cases of systemic lupus erythematosus gave a positive SCAT. Among those in whom the test was positive, articular or peripheral vascular lesions or both were prominent, whereas in patients without this lesion, with the disease affecting mainly the skin or kidneys or other viscera, the SCAT was often negative.

Positive tests were obtained in 16 (41 per cent) of 39 cases of systemic sclerosis. Again, high agglutinating titers tended to be associated with vascular and articular lesions, and negative tests were found in patients who only had scleroderma.

About 40 per cent of positive tests were also found in a group of patients, mostly women, with digital endarteropathy. This group had developed rapid occlusion of the digital and other arteries associated with mild constitutional illness at the onset, they had severe Reynaud's phenomenon and nutritional lesions of the finger pulps, but they had no diffuse sclerosis and no articular lesions. The SCAT was usually negative in other forms of arterial disease and in dermatomyositis. A positive test was found in only 6.7 per cent of sera from 1392 patients with other forms of arthritis, though many of them, such as those with atypical spondylitis, Reiter's disease, and psoriatic arthropathy, had severe inflammatory erosive polyarthritis which resembled rheumatoid arthritis in many respects.

The test was performed in 190 patients with uveitis which is often regarded as a feature of rheumatoid disease. Positive results were obtained in only 10 (5 per cent), and 6 of these had clinical evidence of rheumatoid arthritis. There does not therefore appear to be any association between uveitis and the rheumatoid serum factor.

Positive SCAT results were found in 5.7 per cent of 1165 sera from a random sample of the adult population of a Lancashire town. In this population positive tests were fairly evenly distributed between the sexes and throughout the age groups tested although the proportion of positives was somewhat higher in the older and lower in the younger subjects. Seven of the positive cases showed no clinical evidence of rheumatoid arthritis. However, definite radiological signs of rheumatoid arthritis were found in the cervical spine or feet of several of these. In a further investigation of a random population sample of 428 individuals aged 55 to 64 years, radiologic appearances of this type shows a significant association with positive results in the SCAT, but they were not often associated with other clinically recognizable evidence of rheumatoid arthritis. It would thus appear

that a proportion of positive tests in the SCAT may be associated with rheumatoid changes in the joints which may be either symptomless or of such a nature that they would not be generally recognized as rheumatoid by current criteria. Apparently false-positive results in the SCAT should therefore be accepted with reserve, at least in the 55- to 64-year age group.

In the population studied positive tests showed a significant degree of familial aggregation, being found in about 20 per cent of 94 blood relatives of propositi with positive tests. The presence of a positive SCAT may therefore be genetically determined. If this is so, it may represent an index of some inherited metabolic defect which predisposes the individual to develop certain pathologic lesions which from this point of view should be described as features of rheumatic disease.

It is, however, likely that the disease process itself contributes to the amount of rheumatoid factor found in the serum at any given time. Environmental factors precipitating disease activity are probably important and might occasionally produce articular disease and a positive SCAT in patients not genetically predisposed.

From the study of patients in hospital it is clear that a positive SCAT is very closely associated with the rheumatoid necrobiotic nodule and a certain type of erosive polyarthritis of the limb joints and upper spine. On the other hand, there are clearly many forms of erosive polyarthritis which are not associated with a positive SCAT, and these would by definition be excluded from our concept of rheumatoid arthritis.

As seen, high titers in the SCAT may also be associated with certain vascular lesions which may occur independently or as a part of diffuse connective-tissue disease (systemic lupus erythematosus and systemic sclerosis, for example). These conditions are relatively uncommon and their relationship to the rheumatoid serum factor and the more common articular and nodular manifestations of rheumatoid disease requires further investigation. There may also be other as yet undefined lesions which might be brought to light by a study of individuals with a positive SCAT and their relatives.

Comment: The observation that the rheumatoid serum factor apparently is not important in a large series of uveitis patients certainly differentiates this group from those patients with rheumatoid arthritis in whom this factor usually shows a relatively high titer. Granted that the mechanism of agglutination and the nature of the rheumatoid agglutinating factor is not fully understood, it certainly does appear that there is very little relationship as far as this test is concerned between rheumatoid arthritis and uveitis.

IRVING H. LEOPOLD

OPHTHALMOLOGIC ASPECTS OF PORENCEPHALIC CYSTS

RICHARD K. LANSCHE, THOMAS P. KEARNS AND HENRY W. DODGE

The Sections of Ophthalmology and Neurologic Surgery, The Mayo Clinic, Rochester, Minnesota

Proc. Staff Meet. Mayo Clin., 1958, *33:* 664–670

One of the diagnoses which must be considered in patients with symptoms suggesting the presence of an intracranial mass is a porencephalic cyst. Ophthalmologic symptoms and signs will often suggest the presence of that disease and emphasize the need for definitive surgical confirmation of the diagnosis. Since it is a benign cerebral disease, the recognition of a porencephalic cyst is important in determining the prognosis and treatment of patients in whom it occurs.

The designation "porencephalic cyst" has undergone many changes in meaning since it was first defined by Heschl on the basis of cases reported from 1859 to 1868. In recent years, however, most clinicians have tended to refer to any cystic cavity in the brain substance other than a cystic brain tumor or abscess by the term "porencephaly" whether or not it communicates with the lateral ventricles and the subarachnoid space. The primary cause of porencephalic cysts has been variously considered to be inflammation, trauma, vascular dysplasia, thrombosis, embolism, or neuronal dysplasia. There is probably no single cause for this disease. Similarly no age group of patients is exempt, but most of the reported cases have occurred in persons less than 25 years old.

The clinical syndrome which suggests the possibility of porencephalic cyst has been reported to be characterized by a history of birth injury, a failure of half or part of a half of the body to develop fully, motor and sensory changes in the hypoplastic parts, and jacksonian convulsions. Symptoms of this kind predominate in many cases, for the cavity often occupies a central region of the brain.

The case reports of seven patients, aged 10 to 55 years, seen at the Mayo Clinic, which are given in full by the authors, emphasize the prominent neuro-ophthalmologic symptoms that may be associated with porencephalic cysts. Homonymous hemianopsia was present in each case. Four of the patients were totally unaware of their visual field defect and only one of the remaining three patients was specifically conscious that the visual difficulty was due to a visual field loss. Recovery to normal visual fields occurred in two patients after neurosurgical procedures—ventriculography in one and porencephalo-ventriculostomy in the other. Three patients had strabismus and another had petit mal convulsions during which the eyes and head turned toward the side. The visual acuity of three eyes in two patients was reduced below that explainable by uncorrected refractive errors alone, and the optic nerve head of each of these three eyes was pale. Choked disks were present in each eye of one patient, and mild pallor of previously choked disks produced by a brain tumor was observed in another patient. Nystagmus was present in one patient, but was thought to be due to anticonvulsant medication.

Recovery to normal visual fields after surgical treatment, as noted in two patients, seems to be the exception and not the rule.

Comment: It is interesting to note in the case summaries given by the authors that all four of the children with porencephaly had a convulsive disorder as a presenting complaint, and two showed mental retardation. Two of them gave good evidence of birth injury by history. The ophthalmologic symptoms and signs were of help in the general evaluation, but primary brain injury was the more important suspicion in all four.

Of the three adult patients, one required direct exploration for diagnosis, another required ventriculography, and the third developed the porencephalic cyst after previous brain surgery. The only common factor was homonymous field loss as a part of the neurological findings.

Therefore it is unlikely that a primary diagnosis of porencephalic cyst will be made by the ophthalmologist, but certainly the presence of homonymous hemianopsia, ocular palsies, and optic nerve changes should dictate thorough neurosurgical evaluation.

JOHN WOODWORTH HENDERSON
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PHARMACOLOGY

LOCALLY EMPLOYED ANTIBIOTICS ARE SOMETIMES EXTREMELY HARMFUL IN OPHTHALMOLOGY

JEAN SÉDAN

Marseille, France

Ann. ocul., 1959, *192:* 445–453

In 1957 Redslob published a clinical note in *Annales d'oculistique* with a warning that antibiotics should not be considered a panacea in ophthalmology. He stressed the fact that according to his experience the old and proved remedies such as mercury, silver, and zinc preparations should frequently be resorted to; zinc, for example, was never replaced in the effort to combat the diplococcus of Morax-Axenfeld.

Since the author is in a position to supplement this information by hitherto unpublished material, he has chosen to express his position more strongly, as shown in the title of the present article. This is, of course, not intended to contest the immense services rendered by local application of antibiotics in the vast majority of cases, but rather to show that in some special cases the picture is less rosy.

Three cases of punctate keratitis and corneal ulcers caused by treatment with antibiotics are presented. Such cases are rare and heal rapidly when treatment is discontinued; but in two out of three cases a marked and permanent impairment of visual acuity was caused. All these cases occurred in patients who had been submitted to antibiotics treatment during several treatment periods which were prolonged or rather prolonged. In two out of three cases the patients had been successively treated with different antibiotics. The morphology was identical and the patch tests were positive.

The cases were collected over a period from 1952 to 1958, and allow some general observations: Serious ocular incidents due to local antibiotics are rare, while cutaneo-mucous allergic reactions are relatively frequent. As soon as the treatment is discontinued, recovery is rapid and usually complete, though in the cases presented here two out of three cases showed a marked and permanent impairment of visual acuity. Their morphology is almost a constant one: corneal puncture, confluent in some points where a grayish ulcerous lesion is produced. The extreme confidence of the patients in this type of treatment is often the cause of excessive duration of the therapy, sometimes over more than a year. This attitude is frequently found and dangerous. The devotees tend to turn to various agents, often prescribed by successive ophthalmologists faced with the failure of a previous prescription. The patients are very reluctant to find themselves deprived of their favorite medication, especially if the patch test is momentarily negative. In their opinion the failure of their treatment is the fault of the physician who could not find the suitable antibiotic.

On the other hand, the author wishes to mention the recent aversion to antibiotics, in the opinion of physicians as well as of the public. This should be combatted since it would be as harmful or more harmful, if generalized, than the above-mentioned extreme confidence. It is the physician's task to utilize the immense benefits conveyed by antibiotics and to palliate their few hazards, which is an easy job. They should be well known and well handled.

Comment: This is a further warning concerning the possible sensitivity reactions to locally employed antibiotics. Fortunately such instances are rare, but since they do occur, we must be alert and use antibiotic substances locally only when necessary and preferably for short periods.

IRVING H. LEOPOLD

CALCIUM TREATMENT FOR INEFFECTIVE RESPIRATION RESULTING FROM ADMINISTRATION OF NEOMYCIN

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J. A. M. A., 1959, *170:* 943

A case is reported in which administration of calcium produced reversal of respiratory efficiency occurring after intraperitoneal administration of neomycin.

The patient was a 1-day-old white male infant scheduled for laparotomy because of suspected intestinal obstruction. After intravenous injection of 0.1 mg. of atropine, anesthesia was induced with 10 mg. of 5 per cent sodium Pentothal solution and continued with cyclopropane given endotracheally. Respirations were controlled with a semiclosed technique, and relaxation was provided by intermittent doses of succinylcholine (total, 40 mg.). A side-to-side anastomosis to correct atresia of the small intestine was performed; the procedure required 2½ hours, and to facilitate closure a further 10-mg. dose of succinylcholine was given. At this time approximately 100 mg. of 0.5 per cent neomycin solution were placed in the peritoneal cavity. Within 5 minutes extreme flaccidity of the abdomen and limbs was noted, and no spontaneous respiratory movements took place for 30 minutes. When artificial respiration with oxygen was discontinued the infant became intensely cyanotic. Transfusion of 65 cc. of whole blood and injection of 70 mg. of caffeine in divided doses produced no improvement. Three hours after the operation, the infant's condition being unchanged, 200 mg. of a 10 per cent solution of calcium gluconate was injected slowly, with dramatic improvement, and removal of the endotracheal tube was possible after 30 minutes.

Nine days later another laparotomy became necessary to revise the anastomosis and make a jejunostomy. The same anesthetic technique was used for the 3½-hour procedure, except that 100 mg. of succinylcholine were used. No neomycin was instilled into the peritoneal cavity, and no respiratory difficulties were encountered. In view of the second operation, the possibility seems unlikely that the respiratory depression after the first operation was due to the anesthetic agents and relaxant used.

The exact mode of action of the calcium gluconate in reversing the respiratory depression is not known, although direct action on the myoneural junction is indicated.

Comment: Neomycin is a very effective drug for many forms of intraocular infection. Sorsby has recently stressed the importance of not overlooking this agent as a therapeutic aid in management of intraocular infections. However, the drug does have systemic toxicity. It can produce respiratory depression probably due to its curare-like action at the myoneural junction. In addition to its oral and renal toxicity, apparently neomycin can produce this blockade at the myoneural junction which can at times be quite dangerous to the patient. Naturally, if such a complication does occur, artificial respiration and general supportive measures are necessary and one can try the injection of 200 mg. of 10 per cent solution of calcium gluconate intravenously at a slow rate. Fortunately the complication is a rare one but anyone who uses this agent, even subconjunctivally, must be prepared for this hazard.

IRVING H. LEOPOLD

A CRITICAL REVIEW OF THE EFFECTS OF SALICYLATES ON PITUITARY-ADRENAL FUNCTION

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Postgrad. Med., 1959, *25:* 152–155

Salicylates are effective anti-inflammatory and analgesic medications for the treatment of a wide variety of arthritic conditions. With the advent of cortisone and corticotropin, the similarity of therapeutic response between these preparations and salicylate administration in certain patients suggested that the long-sought mechanism of action of salicylates might be pituitary-adrenocortical stimulation.

However, the evidence in favor of the adrenal-pituitary stimulation to account for the antirheumatic effects of salicylates is meager and concerned with unusually high nontherapeutic doses in rats and guinea pigs, the unconfirmed eosinopenic responses in man, and questionable alterations of steroid blood and urine

levels. On the other hand, considerable evidence has accumulated to negate any hypothesis that the anti-inflammatory and antirheumatic effects of salicylates are mediated through the pituitary-adrenal system.

Many drugs, such as aminopyrine, gentisic acid and cinchophen, exert marked antirheumatic effects and yet do not alter pituitary-adrenal function in animals. Animal and clinical experiments indicate that the effects of salicylates are not only unlike cortisone or pituitary stimulation but are also exactly opposite. Adrenal function is not required for salicylate action. And therapeutic doses, either single or multiple, exert no effect on plasma level of 17-hydroxycorticosteroids in normal adults, patients with acute rheumatic fever, or patients with rheumatoid arthritis.

The bulk of evidence to date, attained by newer and more accurate techniques, does not support the hypothesis that salicylates exert their antirheumatic and anti-inflammatory effects secondary to alteration of the pituitary-adrenal system. Regardless of mechanism of action, salicylates are effective, safe medications for the symptomatic relief of a wide variety of arthritic conditions.

Comment: Ophthalmologists, as others, have been under the impression that salicylates are effective as anti-inflammatory agents most likely through the mechanism of pituitary adrenocortical stimulation. It is stimulating and even somewhat disturbing to note that, as evidence accumulates, salicylates may not be working through this mechanism. The fact that salicylates are helpful as a form of nonspecific medication in a variety of ocular inflammatory disorders has been established by years of clinical testing. It would appear that further pharmacologic studies are required to definitely pin down the exact method by which these agents are producing their ocular antiphlogistic effects.

IRVING H. LEOPOLD

PHARMACOLOGICAL STUDIES OF PYRIMETHAMINE (DARAPRIM) IN MAN

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A. M. A. Arch. Ophth., 1959, *61:* 73–78

A study of pyrimethamine (Daraprim) was made to observe the pharmacology in humans maintained on the drug. Satisfactory antimicrobial therapy is difficult in the treatment of toxoplasmosis. To determine the therapeutic value it is necessary to attain the highest concentration in the serum without exceeding toxicity levels.

Nineteen patients being treated with pyrimethamine and sulfonamides were

hospitalized and divided into three groups for observation. Group I was given 25 mg. of pyrimethamine twice daily from the onset of therapy. Group II received 100 mg. of pyrimethamine twice the first day and 25 mg. twice daily thereafter. Group III consisted of patients who developed hematologic signs after receiving either Dosage Regimen I or II.

Medications were given on the same time schedule. Drug administration and withdrawal samples were recorded daily. Concentration of pyrimethamine in the serum was determined by the use of folic acid as described by G. H. Hitchings, Symposium on Daraprim: Daraprim as an Antagonist of Folic and Folinic Acids, Tr. Roy. Soc. Trop. Med. & Hyg., 1952, *46:* 467–473. Standardization curves and serum blanks were made on each of the groups.

The study showed considerable variation from patient to patient. In Group I, all eight patients differed in degree of absorption or elimination. Although concentrations of pyrimethamine rose gradually, variations were from 0.13 mg. per 100 ml. to 0.44 mg. per 100 ml. Upon cessation of therapy more than a week is required for elimination of the drug from the blood.

Group II showed that the stable high drug level was attained about two weeks earlier with no appreciable increase in toxicity. The final concentrations in this group were similar to those of Group I.

Aqueous humor, taken one week from onset of therapy from five patients with serum levels of 0.1 mg. per 100 ml. or higher, revealed less than 0.005 mg. of pyrimethamine per 100 ml. in all samples despite the presence of cells and flare in the anterior chamber. Pyrimethamine acts on the Toxoplasmas only when they are actively dividing within the cells. Retinal concentration determines the efficacy of the drug. Aqueous concentration seems unrelated to the retinal concentration.

Present evidence indicates toxicity is dose-related. It is desirable to determine whether the patient developing bone marrow depression has a higher serum level of the drug and apparently absorbs more. Patients with bone marrow depression had 1.34 times as high blood levels of pyrimethamine as the patients not showing evidence of hematopoietic dysfunction.

Results of the serial serum pyrimethamine (Daraprim) revealed marked differences in concentrations with patients given the same therapeutic regimen. Excretion of the drug is similar on all patients regardless of the dosage received. Blood level differences were secondary to absorption of the drug rather than a difference in elimination. The hematologic toxicity patient has a higher serum level than the nontoxic patient. Serum pyrimethamine concentration level requires about two weeks unless a "loading dose" is given. A stable blood level is achieved when the serum concentration is sufficiently high to equal intake and elimination. The problem of treatment is increased inasmuch as the organisms may be resistant; they may be resistant to the concentration obtained in the tissue or they may not be multiplying as to be influenced by the drug.

Comment: This paper by Kaufman and Caldwell of the National Institutes of Health and the earlier one of Choi of the Wills Eye Hospital, demonstrate that one cannot always be guided by clinical experience in selecting the proper dosage of a new therapeutic

agent. Dosage schedules for chemotherapeutic agents and antibiotics in ophthalmology have to take into consideration many factors including the penetrability of the blood aqueous barrier, the ability of the drug to be absorbed in the gastro-intestinal tract, and its rate of excretion. It is apparent that many of the dosage schedules which have been reported in clinical studies to date have been on the low side according to the penetration analyses done by Dr. Choi and now by Kaufman and Caldwell. The dosage schedule which we have employed at the Wills Hospital on the basis of Choi's work has consisted of 150 mg. in divided doses the first day, 100 mg. the second day, and a maintenance dose of 75 mg. for the first week. This is practically the same schedule as Dr. Kaufman is recommending here. Such a schedule of a high loading dose will offer the best chance of overcoming the actively growing organisms, of possibly affecting the more resistant types of organisms and those which multiply slowly.

The problem of management of toxoplasmic uveitis is not simple. It is still not an easy task to establish this as an etiologic diagnosis. One cannot be certain that failure to obtain a therapeutic benefit will allow one to eliminate Toxoplasma as an etiology, for the dosage schedule might not permit high enough concentrations to reach the infected tissue. The organism may be resistant to the concentration that is obtained in the tissue, it may not be multiplying rapidly enough to be influenced, or it may be resistant. One can reduce to a certain extent these limiting features by using high dosage schedule as recommended by Choi and by Kaufman and Caldwell. The danger of hematologic toxicity is considerable, particularly with the higher dosage. These patients on the higher dosage schedule must therefore be watched closely for toxic signs.

It must be realized that the ocular tissue which is involved by the organism is essentially the retina, and concentrations in the retina do run higher than those in the ocular fluid and tend to fall closer to those found in the serum. It would be helpful if other drugs could be obtained which would have greater effect on the slower growing toxoplasmic organisms and not possess the same toxic features that are encountered in Daraprim. At the present time at Wills Hospital spiramycin is under investigation for this purpose.

IRVING H. LEOPOLD

THE ACTION OF ALPHA-CHYMOTRYPSIN ON THE RABBIT CORNEA. IS D. F. P. AN ANTIDOTE?

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Bull. Soc. belge d'opht., 1959, *120:* 543–571

α-Chymotrypsin injected into the anterior chamber of rabbits does not luxate the lens, even after 12 hours. This confirms the observations of Barraquer. However, a bullous formation appeared at the site of penetration of the cornea during the anterior chamber injection of the enzyme.

In 1949, Jansen found that α-chymotrypsin was irreversibly inactivated by

di-isopropyl fluorophosphate (DFP). This inhibition persisted after recrystallization, dialysis, and lyophilization, and was optimal between pH 7.5 and 7.7. β-Phenyl-propionic acid will inactivate α-chymotrypsin. The intracorneal injection of a 1:1000 solution of α-chymotrypsin results in a disorganization of the stroma with necrosis; the epithelium and Descemet's membrane remain intact. A similar lesion evolving more slowly takes place with a dilution of 1:5000. However, neither of these dilutions results in zonulolysis in the rabbit. A solution of 1:1000 and 1:5000 of α-chymotrypsin refrigerated for 48 hours, is still active, though slower acting. The injection of the enzyme into the cornea of enucleated rabbit eyes, immediately postmortem, is without any effect.

The topical application of α-chymotrypsin (1:1000) to the rabbit eye is well tolerated. However, if the corneal epithelium is abraded before the topical application, a bullous formation arises, similar to that seen after intracorneal injection. Subconjunctival and intrascleral injection are without untoward effect. Two drops, five times daily, of 0.01 per cent DFP in oily solution was applied to the eye of the rabbits for 48 hours before the intracorneal injection of a 1:1000 solution of α-chymotrypsin. The instillation of DFP was continued for two days following the injection. There was no appreciable difference in the bullous formation between eyes treated with DFP and control eyes.

However, when the intracorneal injection consisted of a mixture of equal amounts of DFP and α-chymotrypsin, no bullous formation was noted. Using abraded eyes, DFP was found to appreciably impede the action of α-chymotrypsin on the cornea. If α-chymotrypsin is injected into the anterior chamber and Descemet's membrane damaged, bullous formation takes place at the site of the break in the membrane. Of DFP, 1.1 moles are required to neutralize 1 mole of α-chymotrypsin. The practical conclusions of these experiments are (1) Decemet's membrane is an effective barrier to α-chymotrypsin, and (2) the utilization of DFP as a miotic at the end of cataract extraction would probably neutralize traces of the enzyme which has remained after irrigation of the anterior chamber.

Comment: This paper appears at a propitious moment in view of the widespread interest in the use of α-chymotrypsin. The importance of avoiding trauma to Descemet's membrane during cataract extraction, becomes even more imperative if the enzymatic technique of zonulolysis is used. In the same issue an article by Weekers *et al.* (Bull. Soc. belge d'opht., 1959, *120:* 539) analyzed statistically 38 cases with zonulolysis by α-chymotrypsin. A late flattening of the anterior chamber occurred as a postoperative complication in 23.6 per cent of the cases with zonulolysis, whereas in a control series the incidence was only 3.6 per cent. The author felt that in spite of all the precautions taken to rid the anterior chamber of the enzyme, in some cases digestion of the borders of the incision took place resulting in delayed healing, leakage of aqueous humor and a flat chamber. No mention is made of accompanying choroidal detachment. The utility of the inactivation of α-chymotrypsin by instillation of DFP at the end of the extraction is obvious. However, the concentration of DFP in the eye would have to be sufficient as 1.1 moles are required to neutralize 1 mole of α-chymotrypsin. A study on corneal wound healing after cataract extraction by zonulolysis with and without DFP would be of interest.

JOEL B. CHODOS

THE INFLUENCE OF DIAMOX ON INORGANIC PHOSPHORUS CONCENTRATION IN SERUM AND AQUEOUS OF RABBITS

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J. Jap. Ophth. Soc., 1959, *63:* 580–586

Aqueous humor from the left eyes of pairs of rabbits was combined and analyzed for inorganic phosphorus. Aqueous humor from the right eyes of these rabbits was obtained after intravenous administration of saline solution (1 ml. per kg.) or Diamox solution (30 mg. of Diamox per kg. of body weight) and similarly analyzed.

The values of phosphorus content of aqueous (2.9) and plasma (4.5) and the ratios between the two (0.6) were similar to those found by other authors.

The saline solution caused a slight change in the inorganic phosphorus concentration in both aqueous and plasma, the change in one being accompanied by a change in the same direction by the other. The maximum increase occurred after 3 hours in both plasma (1.5 per cent) and aqueous (1.8 per cent). The maximum decrease (−2.5 per cent) was observed in plasma after 15 minutes and that of aqueous (−4 per cent) after 30 minutes.

After administration of Diamox the phosphorus content of the plasma increased insignificantly but that of the aqueous increased up to 20 per cent at 2 hours and remained high to the 4th hour. From this it is concluded that the effect of Diamox is specific to the aqueous humor and that an important role is played by phosphate in the metabolism of the ciliary body, lens and cornea.

When the results of this study are compared with those of a previous one on calcium, a reciprocal relationship is found to exist between the concentration of inorganic phosphate and calcium 1 hour after injection of Diamox. The calcium content and inorganic phosphate ions in the aqueous increased more or less in parallel. From the fact that the ratio of plasma calcium and phosphorus is 2.85:1 and the percentage change of calcium is 5 per cent, the change of inorganic phosphate ion in the aqueous is one-half that of calcium ion. As the maximum change of inorganic phosphate was 20 per cent, some unknown mechanism such as an enzymatic activity must be considered as well as the ionic product of calcium and phosphorus ions.

It is known that the ciliary body, lens and cornea contain large amounts of carbonic anhydrase. The presence of cytochrome oxidase and the dehydrogenase system has also been reported (Friedenwald). Ito found that not only E.M.P. but also the TCA cycle is present in the ciliary body. Since Diamox is a chelating agent, it must be inhibiting the oxidative phosphorylation that results in the observed increase of inorganic phosphorus. It is also possible that the inhibitory action on the oxidative phosphorylation results in a lack of high-energy phosphate compounds which then causes the inhibitory effect on the active transport mech-

anism. It is generally believed that Diamox inhibits the carbonic anhydrase, with resulting inhibition of aqueous production. The results of the present paper suggest the possibility that Diamox inhibits the energy metabolism of the ciliary body and the production of carbonate ions which then causes an increase of the inorganic phosphate ions.

Comment: The author has demonstrated that the administration of Diamox raises the concentration of phosphate in the aqueous humor of the anterior chamber. Since phosphate is in deficit in aqueous humor as compared with plasma ($C_a/C_p = 0.6$), it is entirely understandable that slowing down aqueous flow would permit better equilibration with plasma and thus reduce the deficit ($C_a/C_p = 0.7$).

To this reviewer it does not seem necessary nor appropriate to draw any conclusion with reference to the effects of Diamox on oxidative phosphorylation, at least as derived from this type of study.

BERNARD BECKER

Pediatric Opthalmology

EDITORIAL

Ophthalmology, as other branches of medicine, has been developing specialists within its own specialty. We have those whose particular bent is surgical or aspects of surgery, others who are interested in pharmacology, others in neuro-ophthalmology, pathology, physiology, and branches of space medicine. Very few of these individuals are certified in more than one subspecialty in medicine. At present, in our specialty, we have only a few individuals who are both pediatricians and ophthalmologists.

The SURVEY has appointed to its Editorial Staff, Dr. Leonard Apt, a certified pediatrician and ophthalmologist. Dr. Apt devotes all of his time to ophthalmologic problems in the pediatric age group. He will review the articles in the world-wide literature that pertain to this subject for the SURVEY.

IRVING H. LEOPOLD

EDUCATIONAL PROGRAMS NEEDED FOR PARTIALLY SEEING CHILDREN

DOROTHY BRYAN

Am. J. Pub. Health, 1959, *49:* 766–770

In the United States today there are approximately 78,000 partially seeing children of school age. Their vision (20/70 or less in the better eye) is too low to enable them to carry on a normal school program but good enough to be used as their chief channel of learning. The National Society for the Prevention of Blindness reported that at the close of 1957 barely 11 per cent of these children were receiving fair educational opportunities. To meet the needs of these partially seeing children, cooperative and itinerant teacher plans have been developed.

The first programs for the care of partially seeing children in the public schools were initiated in 1913. (Before that time these children were, when possible, sent to residential schools for the blind.) Once educators recognized their need for special help there was a rapid growth in the number of public school programs

aimed at meeting these needs. In some of these programs the children were educated in public schools for the handicapped; in others, in segregated classes in the regular schools. There are few programs of these types now in use.

With the realization of the need for preparing the partially seeing child for life in a seeing society by providing him with the advantage of living at home, growing up as part of the community, and receiving an education with his seeing peers, a third and more acceptable program—the cooperative plan—was developed. Under this organizational plan specially equipped resource rooms are established in centrally located schools. Here the child is provided with special training and assistance in that part of his work which requires close and intensive use of vision; he then spends the rest of the day in the regular classroom, where he participates in its activities. Children eligible for placement must have enough vision to depend upon the medium of sight for the acquisition of knowledge and their mental abilities must parallel those of children in the regular grade so that they may follow as closely as possible the curriculum planned for the normally seeing children.

Through such a cooperative plan the partially seeing child can establish his social status by being able to participate in socializing activities that could not be undertaken in a segregated classroom. In many localities this plan seems to have met the current need. Even so, the children are segregated to a degree. Since they must attend the school in which the special or resource room is located, many cannot attend the schools closest to their homes and are not associating with the same groups of children in and out of school. Nor is this plan practical in rural sections where the children are so widely scattered it is not feasible to attempt to transport them to a school maintaining such a program.

To solve these problems the itinerant teacher or contact plan was evolved. This plan takes the needed special help directly to the partially seeing child. He is enrolled in his regular grade in the school he would normally attend, and the itinerant teacher works with him as much as is needed to enable him to carry on the regular school program. In some instances he may need little more than the provision of special equipment, such as large-type books; in others he will need more intensive help. The amount of such help may vary throughout the year and may switch from one area to another. The itinerant teacher may serve more than one school district, thus meeting the needs of rural as well as urban sections.

Because many children can manage if the classroom teacher knows their needs and knows where to turn for guidance in working with them, as much help as possible is given in the regular class. In Illinois such guidance is offered to classroom teachers through its Division of Special Education. The teacher receives an explanation of the child's particular eye problem, and mimeographed suggestions concerning proper seating and good visual environment; visits are made to her and she is encouraged to write for help or advice; large-type books are provided.

Regardless of the plan used, it is felt that more and more emphasis must be placed on the need for the child to be as much a part of his regular grade and school as is possible. All school personnel must have a clear understanding of the way in which the partially seeing child can work and of what should be expected

of him, as well as of the ways in which he can be helped. In addition to the teachers—both special and classroom—the school nurse, counselor, psychologist, and supervisory and administrative personnel have contributions to make to the child's total growth and development.

Given the proper help, the partially seeing child has a successful school experience and by the time he graduates is ready to face the world with confidence. He is a well adjusted, well rounded person and a contributing member of society, able to hold his own in the complex world of adults.

Comment: Dorothy Bryan has correctly emphasized the basic need of partially sighted children to socialize with normal sighted individuals. As emphasized these children need to learn to live with sighted individuals since they are also sighted but at a lower level of efficiency. It is extremely gratifying that the normal sighted children in schools where the third plan is in effect are more than cooperative in stimulating the partially sighted children to become integrated members of the school community.

The ophthalmologist must be an important member of the educational team. He must not only establish the diagnosis but must aid the educator, understand the individual's particular disease and its limitations and educational and visual prognosis.

HAROLD F. FALLS

PROPTOSIS AS THE FIRST SIGN OF ORBITAL SEPSIS

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Brit. J. Ophth., 1959, *43:* 9–12

Three infants developed proptosis in the newborn period as the first sign of infection in the deep orbital tissues before there were signs of local inflammation. Diagnosis was difficult because the patients otherwise seemed healthy and normal.

In case 1 unilateral proptosis developed on the 14th day of life. The globe was displaced down and in but moved in all directions. A small area of bone destruction was seen in the orbit radiograph. The mother had a pustule on her hand. There was no maxillary or ethmoid sinusitis. Surgical exploration of the orbit revealed a retrobulbar abscess. *Staphylococcus aureus* was cultured from the pus. The infant improved after operation and treatment with chloramphenicol.

The second infant was well until the 11th day of life when bilateral proptosis appeared. The infant seemed well during the next several days but was readmitted to the hospital on the 14th day critically ill. In addition to the proptosis there was edema of the lids and conjunctival edema. The pupils reacted to light, the eye movements were normal and the ophthalmoscopic examination

was negative. Antibiotics and fluids were given but the infant died 3 days later. The necropsy examination disclosed a hemorrhagic condition of the lungs, purulent basal meningitis, retro-orbital abscesses bilaterally, and an osteitis of the right petrous temporal bone. *Staphylococcus aureus* was cultured from the brain and the lungs. There was no thrombosis in either cavernous sinus. The respiratory tract was thought to be the origin of the septicemia.

Unilateral proptosis appeared 1 day after birth in the third patient. The pregnancy had been normal. Radiographs of the orbit were negative. No signs of infection of the maxillary or ethmoid sinuses were found. Chloramphenicol was given because a retrobulbar abscess was presumed to be present. The proptosis gradually disappeared during the subsequent two weeks. In the meantime the mother was treated for puerperal fever, although no specific organism was discovered.

Comment: The author of this article has brought to the attention of the ophthalmologist an observation that is well known to the pediatrician. Namely, a newly born infant during the initial stages of a serious infection may seem entirely well. Since there is a distinct tendency for generalization of infection in the newborn, the pediatrician is constantly on the lookout for any sign of local infection. Even in recent years infection has accounted for 10 to 20 per cent of the neonatal deaths. The newly born infant is more susceptible to septicemia than the older child or adult because specific antibodies against the common forms of staphylococci, streptococci, and colon bacilli are not transmitted to the fetus through the placenta.

When an ophthalmologist is confronted with the clinical situation of sudden proptosis in a newborn infant who does not appear to have any disturbance, he probably would consider diagnoses such as retrobulbar hemorrhage, orbital fracture, orbital tumor and so on. We now know of another cause. By keeping this article in mind the ophthalmologist at some future time may be able to do justice not only to the eye problem but may save an infant's life by promptly starting antibiotic therapy. Chloramphenicol, the drug used by the author, is a good initial choice since its broad spectrum of activity is effective against the principal pathogens in the young infant. The clinical response, the results of cultures and sensitivity tests may dictate a change of therapy. The ophthalmologist may not be able to make the diagnosis of orbital sepsis with certainty when the patient is first seen, but fortunately antibiotic therapy would not interfere with the investigation or management of the other diagnostic possibilities.

LEONARD APT

JUVENILE XANTHOGRANULOMA WITH OCULAR INVOLVEMENT

Report of Case

Reza Gharib, Edmund C. Burke and Louis A. Brunsting

Mayo Foundation, Rochester, Minnesota

J. Pediat., 1959, *54:* 109–112

A 4-month-old girl was referred to the Mayo Clinic because of skin and eye lesions of a duration of 2½ months. At 6 weeks of age skin lesions began to appear on the face, chest, trunk and back. They began as small erythematous papules and enlarged to well circumscribed firm, rubbery hard, raised, yellow-pink lesions ⅛ to ⅓ inch in diameter. At 3 months of age the left eye began to tear excessively and appear inflamed.

On admission the ophthalmologist found macrophthalmia of the left eye, an edematous cornea, and a small blood clot in the pupillary opening. The ocular tension seemed normal to him. The right eye was normal.

The peripheral blood count and radiographs of the thorax and head were negative. The cholesterol concentration was 193 mg. per 100 ml. of serum.

Examination of a biopsy specimen of one of the skin lesions revealed histiocytes, many capillaries, and giant cells of the Touton and foreign body types. Intra- and extracellular deposition of fat was demonstrated by fat stains.

The diagnosis of nevoxantho-endothelioma (juvenile xanthogranuloma) with involvement of the optic globe was made. The ophthalmologist was of the opinion that since the infant's eye was painless and possessed a benign lesion which tends to regress, surgical treatment was contraindicated.

Correspondence with the infant's mother 7 months after the initial examination indicated that the skin lesions were getting smaller and that no new lesions had appeared. The left globe still appeared "swollen", the iris discolored, but the pupil was visible.

Comment: The association of ocular and skin lesions of nevoxantho-endothelioma has been recognized only in the past decade. Six cases of the entity have been described at the time of this comment, and most of these since 1956. The relative rarity of the disease should not detract from the importance of the physician's knowing about the ocular aspects. Prompt diagnosis and new therapeutic measures have led to the preservation of useful eyes. The entity is probably more common than is realized. In addition to the reports that have appeared in the literature at the time of this writing, Maumenee and Longfellow have a report of 2 cases in press, and at least 12 additional unreported cases have been seen by other physicians throughout the country and at the Armed Forces Institute of Pathology.

Since there are so few reports in the literature it would have been advantageous to have had a more detailed description of the eye findings of the patient presented in the above article. I suspect that the case was similar to most of the others described in that the eye lesion is a granulomatous infiltration of the iris and ciliary body, and that the history is characterized by spontaneous, recurrent anterior chamber hemorrhages, discoloration

and thickening of the iris, and secondary glaucoma in a young infant or child. A report of an epibulbar nevoxantho-endothelioma was made by Cogan, Kuwabara and Parke (A. M. A. Arch. Ophth., *59:* 719, 1958).

Although the nevoxantho-endothelioma lesions tend to regress spontaneously and are benign histologically, the lesion in the eye because of its location in the anterior uvea cannot be regarded as benign. Infiltration of the iris angle with cells, the inflammatory reaction, and recurrent hyphema may lead to secondary glaucoma. Because of the possible serious effects of this new growth a few ophthalmologists have taken a more positive approach to therapy. Newell (A. M. A. Arch. Ophth., *58:* 321, 1957) was able to control the glaucoma in one of his cases by performing a trephine operation. Dr. C. Hedges Jr. (Am. J. Ophth., *47:* 683, 1959) used superficial x-ray therapy on a nevoxantho-endothelioma lesion of the iris in an infant with secondary glaucoma and found that the lesions promptly regressed.

Though Hedges is the first author to report on the curative effect of superficial x-ray therapy in ocular nevoxantho-endothelioma Dr. A. E. Maumenee should be given his just credit for originating the idea. In 1954 Maumenee used radiation effectively in ocular nevoxantho-endothelioma in a young child and again in another patient in 1957. Steroid therapy was also used in the treatment of the 2 patients of Maumenee and Longfellow.

Dr. Maumenee's rationale for the use of steroid and x-ray therapy in ocular nevoxantho-endothelioma was based on the fact that lesions of eosinophilic granuloma and Hand-Schuller-Christian disease (reticulo-endothelioses with a histologic picture similar to nevoxantho-endothelioma) have responded in some instances to this therapy. Maumenee and Longfellow advise using radiation therapy if glaucoma or recurrent hyphema cannot be controlled with corticosteroids, Diamox, miotics or mydriatics. They warn that the total radiation dose (air dose) should not exceed 500 r, and any single dose should be less than 200 r to the lens to prevent radiation cataract.

LEONARD APT

OCULAR SIGNS AND PROGNOSIS IN SUBDURAL AND SUBARACHNOID BLEEDING IN YOUNG CHILDREN

ROBERT W. HOLLENHORST AND HAROLD A. STEIN

Mayo Foundation, Rochester, Minnesota

A. M. A. Arch. Ophth., 1958, *60:* 187–192

This report is an analysis of 47 patients with proved subdural hematoma (31) subarachnoid hemorrhage (10), and subdural hygroma (6) occurring among children 5 years old or younger. The patients were seen and followed during an 11-year interval.

Of the 47 patients, 39 were less than 1 year of age. The high incidence has been ascribed to the poorly developed supporting tissues around the intracranial vessels in infants of this age.

Convulsions and vomiting were the chief presenting symptoms. An enlarging head, paralysis, spasticity and stupor were found in a smaller number.

Ocular abnormalities were the precominant signs in the series—28, or 60 per

cent, of the 47 patients. The finding consisted mainly of numerous zones of subhyaloid and retinal hemorrhage (24 of the 47 patients). In no case did the hemorrhage enter the vitreous body.

Half of the infants and children who had subdural hematoma and 70 per cent of those who had subarachnoid hemorrhage had extensive retinal and subhyaloid hemorrhages. In adults such hemorrhage is a characteristic sign of subarachnoid bleeding but does not usually appear with subdural hematoma.

The blood in the eyes showed signs of beginning absorption as early as 1 week after the intracranial lesions were treated. Healing usually was complete and no traces of the previous hemorrhage remained.

Of the 24 patients who had intraocular hemorrhage 5 had papilledema and 5 had palsy of cranial nerve (3rd N and 6th N); 2 of the 28 patients who had ocular abnormalities had papilledema without retinal hemorrhage, and the remaining 2 patients had palsy of the 6th cranial nerves without retinal hemorrhage.

A positive or possible history of trauma was noted in 23 of the 47 cases. The intracranial bleeding was attributed to a blood dyscrasia in 3 patients.

Of the 28 patients who had ocular abnormalities, 3 died. A total of 23 of the remaining 25 were examined and traced. Of these 8 (35 per cent) had permanent visual handicaps; 7 initially had intraocular hemorrhages and 1 had an isolated palsy of the 6th nerve. The permanent ocular defects included amblyopia, total blindness, optic atrophy, strabismus, and 6th nerve palsy. Only 1 of the 15 traced survivors who did not have ocular defects at the time they sustained intracranial bleeding had permanent ocular damage.

None of the patients had pathologically pale optic disks at the initial examination, although pale disks developed in 2 patients. Of the 8 patients with permanent ocular defects, 6 were known to have experienced trauma.

Comment: The point derived from the authors' study is that prognosis for good vision should be guarded in an infant with a subdural hematoma or subarachnoid hemorrhage who has associated ocular signs (predominantly intraocular hemorrhage), particularly if there is a history of head trauma.

The high incidence of permanent ocular defects reported in this series (8 of 23 patients) is striking. In a discussion of this finding with the neurosurgeons of the Children's Hospitals in Boston and in Philadelphia they stated that in their experience permanent blindness or deep amblyopia was exceedingly uncommon. Their combined series would exceed 500 cases and most of the patients had been followed for 2 to 10 years.

Of course there are many factors that may account for the discrepancy in incidence: the case material, the severity of trauma, the extent of bleeding, the duration of illness, and the promptness and type of neurosurgical treatment. Regardless of the true incidence, as far as the individual patient is concerned it seems essential that one of the attending physicians should include an examination of the eyes in the follow-up physical examinations of any child who has had intracranial bleeding, especially if intraocular hemorrhage, papilledema, or cranial nerve palsies were associated findings. In this way the physician will be able to explain a pale optic disk, an amblyopia, a strabismus—eye disorders which if detected for the first time years after the illness, could present a diagnostic problem to the pediatrician or ophthalmologist.

LEONARD APT

Space Ophthalmology

AIR-TO-AIR TRACKING DURING CLOSED-LOOP CENTRIFUGE OPERATION

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Aviation Med., 1958, *29:* 794–804

In the design of any new air weapons system it has become common practice to conduct preliminary evaluations of the system with simulators. A serious limitation of simulator investigations of human performance is the absence of any of the complications which exist in aircraft as the result of the aircraft motion. Linear and angular accelerations can reduce the efficiency of motor performance and may completely incapacitate a pilot for performance of his task.

The effects of acceleration on performance can be studied in a laboratory situation by the use of a centrifuge. When acceleration patterns are predetermined, they are not in any way influenced by the subject's performance. But the various motions and accelerations to which a pilot is exposed are largely determined by his own control manipulations. Hence, there is an interaction between his performance and the g to which he is subjected.

Performance was studied on the centrifuge in a simulated, air-to-air tracking situation. Centrifuge motion was controlled by manipulations of aircraft controls located in the centrifuge gondola in such a way that subjects were exposed to acceleration patterns which were appropriate to their performance in the tracking situation. It was found that performance of the tracking task showed a statistically significant decrement under experimental conditions as compared with control conditions with the centrifuge stationary. A score which represented flight co-ordination showed a statistically significant improvement under experimental conditions as compared with control conditions.

All subjects performed better, on the average, in vertical tracking when the centrifuge was at rest than when under acceleration. Four out of five subjects showed slightly better performance in horizontal tracking under control conditions, but the differences were small.

The amount by which vertical tracking error is increased during exposure to acceleration is small but it must be remembered that the disturbance frequencies used in the tracking tasks were extremely low and tracking scores were accumu-

lated over only 1-minute periods. Under these conditions there was considerable variability in the difficulty of the tracking task from one run to another. With the small number of runs which were made for each subject this variability tended to reduce the sensitivity of the scores as an index of the detrimental effects of acceleration.

It must also be remembered that in the present experiment the maximum positive acceleration to which subjects were ever exposed was $2\frac{1}{2}$ g. This is considerably less than the maximum accelerations encountered in aircraft and it may be expected that in the future experiments in which higher maximum levels of acceleration are used, effects on performance will be more dramatic.

It has been suggested that man in a sensory-motor performance task may be regarded as a system with limited band width. In the present context, this concept provides an alternate way of discussing the results. When the nature of the task is changed so that flight coordination becomes more important, it can be improved only at the expense of some other aspect of performance, in this case vertical tracking.

Comment: Of all the stresses to which man will be exposed in space flight the one most likely to be incapacitating to his visual function is acceleration of some type. The study reported here indicates a decreased tracking capability under g forces which may be due in some degree to decreased effectiveness in the visual component of the performance task. The decrement in vertical tracking performance is suggestive.

VICTOR A. BYRNES

Miscellany

This section will be devoted to questions and answers, brief abstracts, comments and the like. Each letter must contain the writer's name and address, but these will be omitted on request.

TRAINING

MEDICAL EDUCATION AND AMERICAN SPECIALTY BOARDS*

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J. M. Educ., 1959, *34:* 555–560

In the course of unprecedented advances in scientific knowledge during the past century it gradually became evident that, if a physician were to master the ever increasing amount of background information and the skill essential to its optimum clinical application, it would be necessary for him to confine himself to some particular aspect or "field" of medicine. Thus specialization began.

In the United States, the increasing demand for specialty training at first was met by the development of what were soon to become known as residency training programs in the clinical services of medical school-connected hospitals. As formally organized educational institutions, however, the medical schools exerted no direct control over these graduate teaching units. They were subject only to the planning of the individual chiefs of service and the limitations imposed by the facilities available in the hospitals where they were located. Naturally, this led to great variation in content, duration, and type of experience offered. The situation was still further confused by the inauguration of specialty training in nonmedical school-connected hospitals, the visiting staff members of which early recognized the value of having a house staff composed of able, highly motivated trainees for specialty practice.

At this time the goal of recognition as a "specialist" could be reached by a number of different routes, some of them almost unbelievable. Any physician who developed interest and skill in some field of medical practice could restrict his work to it and call himself a specialist. A young physician could serve as an assistant to anyone having a specialty practice and by means of this "preceptorship" training become a specialist himself. Or, a recent graduate could go directly from his internship to residency training of indeterminate quality, and of a duration dictated solely by his own opportunities and whims, and then feel qualified to practice a specialty. Moreover, unfortunately, any physician could spend a few

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months, or even a few weeks, in a clinic abroad—while enjoying the cultural, gustatory, and entertainment advantages of some European capital—and then return a specialist. So patients, hospitals, and even the medical profession itself had no good means of distinguishing a bona fide specialist, with long years of superior preparation, from a self-entitled specialist with little or none.

The medical schools, fully occupied with raising their own standards and with no time or funds for new ventures, showed little interest in this matter, even though it was their own faculty members who were responsible for the vast majority of the better residency training programs that were fast developing. As time passed, there came into existence a number of graduate and postgraduate schools of medicine, but these failed to take hold in comparison with the residency training programs.

The first organized effort to control this unhappy situation was the incorporation in 1917 of the American Board of Ophthalmic Examinations (later changed to American Board of Ophthalmology).

In 1920, the Council on Medical Education and Hospitals of the American Medical Association organized fifteen committees, of nine members each, to study and "recommend what preparation was deemed essential to secure expertness in each of the Specialties" (5). Out of these committees emerged the pattern that was to be followed in the establishment of the nineteen Approved American Specialty Boards now in existence. Thus, the Boards arose primarily in response to the need for a mechanism to prevent dangerous shortcuts to specialty practice.

Then, because of the additional need for some central agency through which these American Boards could meet and consider their mutual problems, the Advisory Board for Medical Specialties was organized in 1934 (1). Although "advisory" in character, all American Boards are members, and this alliance serves as a strong deterrent to the organization of stray examining boards and the use of the title "American Board" by unofficial groups. The Advisory Board maintains a close liaison with the Council on Medical Education and Hospitals.

That is the story of how and why American Specialty Boards came into being. My purpose now is to explore their organization and functions; their relationship to, and effect upon, hospital-centered residency training programs; the methods by which they determine the competence of those whom they certify; and their role in medical education.

ORGANIZATION

All the nineteen Specialty Boards in existence in 1958 are incorporated. A "Board" consists of from nine to 23 "Members" or "Directors" (six have nine members, six have twelve) who are appointed for a definite term. Members are selected in various ways, but in the majority nominations are made by specified societies and election is by the Board. The "nominating societies," usually three or more in number, include the appropriate "Section" of the American Medical Association. The other societies include the national organizations in the particular specialty. Most Boards have Secretaries or Executive Secretaries who serve for an indefinite term and who may or may not be "Members" of the Board. In a

few of the larger Boards (in terms of number of certificate holders) these are full-time appointments.

Those who hold a certificate of a Board are known as "Diplomates" (sometimes loosely and improperly called "members"). All Boards make it clear that the certificate is not to be considered as a "license to practice."

The Boards are composed of volunteers who serve without recompense. One Board estimates that its members spend from 20 to 22 days away from home each year and must in addition carry out a good many duties at home. This is no mean sacrifice for a practitioner or a part-time faculty member, and Board Members richly deserve commendation from the profession at large.

By their very nature Specialty Boards are loosely organized. The terms of old members expire, new ones are appointed. It is little wonder that at times they have not understood clearly their prescribed duties. Exactly what is their function?

FUNCTION OF SPECIALTY BOARDS

Each Board publishes a Statement or booklet setting forth, among other items, its function as conceived by that Board. Through these documents runs a common theme that may be expressed briefly as follows:

To establish minimal educational and training standards,

To determine whether candidates have received adequate preparation as defined by the Board in question,

To conduct examinations of eligible candidates,

To certify, as competent to practice the specialty, those physicians who have met its requirements and passed the examinations.

How well have the Boards fulfilled their functions?

THE ESTABLISHMENT OF EDUCATIONAL AND TRAINING STANDARDS

The Boards have first decided upon the amount of time that a candidate must spend in residency training and in practice or further study before becoming eligible to take the examination for certification. They have then turned their attention to evaluation of the residency training programs offered in different hospitals and, to this end, have set up Residency Review Committees in conjunction with the Council on Medical Education and Hospitals, and usually with at least one of their "Nominating Societies." These Committees have established minimal standards, and, through the staff of the Council, they conduct a site evaluation of every hospital residency training program that desires approval. On the basis of information so collected and the recommendation of the evaluator, the Committees then approve or disapprove the hospital for training in the specialty in question. Hospital programs are reviewed every 2 or 3 years. The list of approved programs under the name of the hospital are published each year in the Internship and Residency Number of the *Journal of the American Medical Association*.

While it is difficult to be certain of the effect of Specialty Boards on the development of residency training programs, it is not difficult to believe that it has been considerable, for residency training has become the preferred method of

preparation for specialty practice by all Boards, and, since a stated number of years of training in residence has been prescribed, many physicians desiring Board certification have no doubt been stimulated to comply with the regulations. Whatever the cause, the growth of residency training programs has been phenomenal. In the 30-year period from 1927 to 1957 the number of hospitals with approved residency training programs has increased from 270 to 1199, and the number of residency appointments offered has grown from 1,699 to 28,528 (4). Meanwhile, graduate school courses, whether independent or under the auspices of a school of medicine, have with a few notable exceptions failed to flourish or have disappeared. Their total output of physicians has always been very small when compared with that of residency training. During the same 30 years, preceptorship training has essentially disappeared. Training abroad, except for a small number of internationally known clinics, has not been accepted by American Boards and has ceased to be an important factor. On the other hand, residency training in American hospitals for graduates of foreign medical schools has become very common, estimates indicating that foreign graduates represent about 20 per cent of the total residents in training.

The concept of learning, through a properly organized and progressively graded responsibility for the continuing care of sick patients under the supervision of attending physicians who are themselves responsible for the care of patients on the service, has become the heart of residency training in the United States. This principle has been espoused strongly by the Boards, and they have contributed to its development through their requirement or preference for residency training as a forerunner to certification.

There is no adequate basis for comparison of residency training with other methods as preparation for specialty practice. One can only say that it has been extraordinarily successful, if judged by the level of specialty practice in the United States as compared with that in other countries, by the present position of American Medicine abroad in relation to its position 50 years ago, and by the popularity of residency training in the United States among foreigners as a means of preparation for practice in their native lands. The Boards would therefore seem to be fully justified in requiring a specified number of years of residency training prior to examination for certification.

EXAMINATIONS

A discussion of the possible predictive value of examinations in determining the competence of the individual to practice a specialty may be of interest, since all Specialty Boards have adopted them as the final determinant for certification. For practical purposes, examinations represent the best procedure available to external agencies charged with comparative rating of individuals in large groups.

Specialty Boards commonly use two sets of examinations, written and oral. The written examination serves as a screening device. Given first, it must be passed before the candidate is admitted to the oral test. Most Boards use an objective type of examination as best suited to the testing of large groups of candidates. When properly designed such an examination is "skewed toward the lower

grades," where it becomes "relatively sensitive in the critical range," where passing or failing decisions must be made. The same test may be relatively insensitive at the upper level, but here exact selection becomes relatively unimportant, since all are obviously qualified (6).

Oral examinations, where the candidate usually comes before a series of individual examiners and where patients may or may not be used, are a form of testing that possesses certain virtues but is unquestionably open to criticism. Critics point out the danger of failing to cover essential important subjects or of concentrating on an area of weakness or, *per contra*, one of special competence of the candidate, the risk of "hobby riding" by examiners, the interaction of personalities leading to a good or poor rapport between candidate and examiner, and to the effect of stress on the candidate's performance.

The advocates of oral examinations admit the validity of the above objections but believe that they can be overcome. A properly structured oral examination should touch on a wide range of topics any of which may be probed in depth if the examiner wishes; it will relegate "hobby riding" to a minimum. The skilled examiner, aware of the pitfalls of interpersonal reactions, discounts the engaging personality of one, admits his lack of rapport with another, and takes into account the excessive degree of nervous tension manifested in a third. Experienced examiners succeed in putting most candidates at ease as the examination progresses, but there are a few candidates who seem to "lose their heads" for its duration. Failure for them may, at first glance, seem unfair, but it should be remembered that a physician must often make his most crucial decisions under circumstances of great stress, so the manner in which the candidate reacts under the pressure of examination may be relevant.

In addition to medical knowledge and to skill in its application, many intangible factors enter into success in the practice of medicine—motivation, energy, drive, the ability to work long hours, attention to duty, empathy with patients, physical health, emotional stability, a happy choice of location, not to mention "good luck" and "a good wife." It would be hard enough to measure a doctor's relative competence in a community under any circumstances and by any means, but to assess the importance of these intangibles would immeasurably compound the difficulties. No matter how well an examination might be designed to measure medical "know-how" at a given point of time, it would not necessarily correlate closely with an estimation of success in the practice of medicine judged a specified number of years later.

The most one can hope to do in a Board examination is to measure the candidate's current fund of medical information and estimate his ability to translate this information into the diagnosis and treatment of disease in his special field. This I believe the Boards accomplish with a relatively high degree of success. I do agree with Meyers (2), however, that the Boards should try to check the results of their examinations "against the evaluation of observers on the scenes of action." The difficulties of doing this in the years of practice have been pointed out, but there is an opportunity to measure performance in the examination against that in residency training because "long-sustained observation and consensus

evaluation by a number of observers" are available through the chief of service and his staff, who incidentally are highly competent to render judgment.

CRITICISMS

Most of the criticisms against the Specialty Boards that I have heard personally have come from those who actually knew very little about the Boards and who tend to hold all Boards responsible for some action taken by one Board at some period of its existence. There is no doubt that at one time or another certain Boards have adopted policies not in keeping with their announced functions. These transgressions of the past have been corrected, however, for in 1955 the Advisory Board for Medical Specialties adopted a set of principles of operation with which it is hard to find fault.

One criticism of a different nature should be considered—the fear that the Boards might exert too much authority over residency training programs. First, it should be realized that the most a Board can do is say that it will grant credit toward certification only to those hospital training programs approved by the Residency Review Committee. This Committee in its turn can withhold approval, which means only that the residents in that hospital will not receive Board credit. In actual practice such approval is withheld only at the lowest level of performance or for gross deficiencies—as, for example, lack of experience with newborns or of outpatient service in Pediatrics. Close control of programs by the Boards would be virtually impossible even if it were not true because of the extent of the operation. In 1957 there were 5,134 separate approved programs involving over 28,000 appointments. To be sure there are several sub-specialties that have only a relatively small number of approved programs, but these are in such highly specialized areas that the number of candidates is small. Meanwhile, the Residency Review Committee representing a Board of average size will have as many as 250 programs scattered throughout the country, while the larger Boards will have more than 600.

FOREIGN MEDICAL GRADUATES

A present-day evaluation of American Specialty Boards in medical education would be incomplete without reference to their role in the training of foreign medical graduates. In 1957, 21 per cent of all residents (interns excluded) were graduates of foreign medical schools (Canadian graduates represented 2.5 per cent of these) (4). Since the majority of these residents will return to their native country, this represents a significant contribution to world medical education by residency training programs in this country. Since American Specialty Boards have contributed so largely to the growth of such programs, the Boards share indirectly in this contribution. A number of Boards now admit to examination foreign graduates who have had residency training in the United States, and if they pass they are issued a foreign citizen's certificate. This procedure is well liked by foreign graduates and unquestionably increases the number who come to this country.

SUMMARY

1. Specialization in medical practice created a demand for training beyond the internship. Residency training programs were developed to meet this demand.

2. American Specialty Boards arose in response to a need for a mechanism that would prevent dangerous shortcuts to specialty practice.

3. Although residency training programs were developed principally in medical school teaching hospitals, the schools have never exerted direct control over them.

4. Board requirements of a specified number of years of residency training in approved hospital programs in order to become eligible for certification have contributed greatly to the growth of residency training programs.

5. The Boards, in conjunction with the Council on Medical Education and Hospitals and certain specialty societies, have established Residency Review Committees which evaluate residency training programs.

6. The Organization of Boards has been described.

7. The Boards have defined their own functions clearly. The examination of candidates for certification is one of the most important of those functions. The nature and value of the examinations have been discussed.

8. The present relationship of the Boards to the graduates of foreign medical schools who are undertaking residency training in this country has been described.

Comment: I cannot speak for the American Board of Ophthalmology, as a whole, but my impression is that the Board would welcome the publication of this, as it clearly defines the objectives of the Board and answers many criticisms which have been raised against the Board from time to time. As a present Consultant to the Board, and a member of the Committee on written examinations, on which I have served for many years, I would emphasize the fact, pointed out by Dr. Mitchell, that the written examination is a screening device designed to eliminate candidates who have not had sufficient training to present themselves for the oral examination, which is still the crucial test of competency in ophthalmology. In its present form the written examination has now been adequately tested by item analysis and statistical techniques which prove that it is an excellent screening device. The time has now come when the oral examination must be similarly investigated and subjected to rigid scrutiny. Methods can be and will be devised to eliminate the weak points mentioned by Dr. Mitchell.

The examination of the American Board of Ophthalmology has always been a good examination, but it can be made better, and the members of the Board are all conscious of this and strive in every way to eliminate weaknesses. It has always been interested in making improvements, and welcomes any suggestions which are constructive.

FRANCIS HEED ADLER

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RECENT MEETINGS

THE OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

ANNUAL CONGRESS—APRIL 9TH, 10TH AND 11TH, 1959

Ophthalmologica, 1959, *138:* 151–153

The 79th Annual Congress of the Ophthalmological Society of the United Kingdom was held at the House of the Royal Society of Medicine, on Thursday, Friday and Saturday, April 9th, 10th and 11th.

Mr. R. C. Davenport, President of the Society, was in the Chair.

Over 300 members and their guests attended, including several distinguished foreign visitors.

In his presidential address, entitled "Facets of Glaucoma," Mr. R. C. Davenport considered the relationship between myopia and glaucoma, recalling that association of the two conditions was not as uncommon as is often supposed. He then discussed the relationship between glaucoma and obliterative arterial disease and its possible etiologic significance.

In the main discussion on "The Swollen Optic Disk" Mr. Desmond Greaves stressed the need of recognizing the wide limits of normal and congenital anomalies and to distinguish them from early pathologic changes. He discussed the vascular arrangement at the nerve head and the absence of any considerable connection between the central artery of the optic nerve and the circle of Zinn on the one hand and the central retinal artery on the other.

He then drew attention to the importance of the degree of swelling of the optic disk and the loss of function, as the relationship between the two gives much help in diagnosis—this point was also referred to by the later speakers, as was the terminology. All agreed that papilledema was an unsatisfactory term especially for universal application to the swollen optic disk, but recognized that its use was so well established that attempts to abolish it were probably unrealistic.

Dr. S. P. Meadows discussed swelling of the optic disk in various clinical conditions, particularly raised intracranial pressure, but said that the latter could not be ruled out merely because the optic nerve was not swollen. The degree of swelling was variable even in cases such as cerebellar tumors, which are particularly prone to early papilledema. He referred to the cardinal importance of the

swollen disk in malignant hypertension and the response of these cases to treatment. He discussed retinal vascular occlusion and degenerative conditions of the optic nerves and their differential diagnosis. He also discussed benign intracranial hypertension and the striking picture which the disks present. Another unusual picture which he showed was of papilledema and retinal hemorrhages in a case of emphysema.

Mr. Charles Cook showed a number of slides which clearly exhibited the histologic changes which take place in swelling of the disk and showed how the retina in the immediate neighborhood was shallowly detached. The course taken by the optic nerve fibers in papilledema and the importance of the cul-de-sac of the subarachnoid space were both demonstrated.

A symposium was held on "The Treatment of Ocular Injuries."

Mr. John Whitwell who considered "Non-Perforating Injuries" felt that their treatment was almost as dull as refractions. He found little to choose between albucid and polyfax as a routine ointment after corneal foreign bodies—the commonest of all injuries. He felt rust rings should be removed early. He made a plea for the admission of all cases of traumatic hyphema and the proper resting of all cases of considerable trauma, particularly in view of the danger of secondary hemorrhage and glaucoma which is very difficult to treat and may lead to loss of useful vision or even of the eye. The operation of choice was cyclodiathermy in those cases where glaucoma did occur. Subconjuncitval Papaverine was suggested as a treatment for commotio retinae. The need to search the retina for tears even in the absence of retinal detachment was stressed.

Mr. M. J. Roper-Hall dealt with "Perforating Wounds" and said that the recent improvement in the treatment of those wounds without retained foreign bodies was probably due to the meticulous suturing of the corneoscleral wounds and the injection of air into the anterior chamber. The latter not only checked that the suture line was water- (or air-)tight, but also discouraged anterior synechiae. Conjunctival flaps had been almost abandoned. He made a plea for the use of magnification so that the surgeon could really see what he was doing—even those surgeons who were not yet so presbyopic as to need reading glasses.

Reposition of prolapsed iris—in very recent injuries—seemed to be justified in some cases.

With reference to intraocular foreign bodies he felt that there was not so much hurry to remove them that accurate localization could be overlooked. It was better to wait a while if proper x-ray or theater facilities were not immediately available. He personally favored the use of a "Mellinger" type magnet especially for posterior route removal, which was the method of choice in most cases, unless the lens was much damaged already.

Diathermy was not necessary to stop detachments after posterior route removal as the passage of the foreign body set up enough choroiditis to do that, but it might reduce the risk of vitreous hemorrhage. With nonmagnetic foreign bodies it was justifiable to wait a week or two to gauge the strength of the ocular reaction as removal of these objects was likely to be very traumatic.

Mr. Giles Romanes spoke on the "Treatment of Eye Burns." He based his

paper on cases treated at East Grinstead. He stressed the need for immediate action to cover the cornea, where there was loss of lid tissue, and he discussed the use of a bipedicle conjunctival flap for this purpose and other possible methods. In chemical burns the cardinal place of immediate and prolonged irrigation was agreed by all.

The Bowman Lecture this year was given by Professor Louis Paufique, of Lyons, on "The Present Status of the Treatment of Retinal Detachment." In it he surveyed the history of detachment surgery since the days of his youth, before Gonin had performed his first successful operation, recalling that even in 1929 Professor Gayet had declared "to wish to treat a retinal detachment one must be either a charlatan or a fool."

Paufique recalled the crude results with Gonin's thermocautery, then Weve's introduction of diathermy and his method of localizing the retinal tears by transillumination; then in 1950 came the operation of Lamellar scleral resection to replace the more dangerous and difficult full-thickness resection of Muller and Lindner, an operation that was elaborated, particularly by Shapland in England and Paufique himself in France, till it has become nowadays the operation of choice in about half our cases. Finally, Paufique dwelt in some detail on the latest advances—of vitreous transplantation (using powdered lypohilized vitreous) and light-coagulation.

In evaluating his latest 524 cases, Paufique recorded a 70 per cent success-rate (a figure that corresponds with most other recent assessments); of those that failed, in 15 per cent the nature of the detachment could be said almost to have precluded a cure, it remained difficult to explain adequately why the other 15 per cent failed. So Paufique then discussed the various factors in the pathogenesis of such detachments and presented impressive histologic evidence of congenital choroidal lesions, which he felt might well be responsible and merit prophylactic surgery.

Of the other short papers that completed the Congress, Mr. R. W. Stephenson assessed "The Use of Miotics in Convergent Squint," especially those that were fully accommodative with convergence excess; and D.F.P. was the drug that had been used in a series of cases with limited success.

Dr. Eric Linner from Goteborg, Sweden, assessed the rate of aqueous flow in disordered adrenal function, where the usual decrease at night was found to be significantly less pronounced.

Mr. Frank Law assessed the Georg Young Threshold Test in the diagnosis of early glaucoma.

Mr. A. G. Cross described some cases of successful treatment of persistent vernal catarrh by the inlay of buccal mucous membrane.

Mr. H. B. Stallard emphasized some important practical points in the early surgical treatment of eyelid injuries.

Mr. Arthur Lister discussed the gonioscopic appearance of the drainage angle in infantile glaucoma.

Dr. F. Papolczy described a plastic repair of cicatricial ectropion by free transplantation.

Brigadier J. D. Welch discussed the ideal layout and organization of an ophthalmic outpatient department.

Mr. Dermot Pierse described a new method for cutting corneal grafts.

Mr. Derek Ainslie reviewed his results in 100 penetrating corneal grafts.

Mr. W. E. S. Bain described the results shown by the recording tonometer recently introduced by Maurice, which allows the subject to move freely while wearing it.

Mr. L. G. Fison gave a pictorial demonstration to illustrate the difficulties in differential diagnosis of secondary retinal detachments and the advantages of binocular ophthalmoscopy.

Mr. P. D. Trevor-Roper considered the evolution of visual artistry, attempting to bridge the gap that separates the nonrepresentational "art" of birds and primates from the representational art of primitive man, in the light of the developmental stages of child art, near-blind painting and blind sculpture.

Mr. F. C. Rodger described his investigation into the effect of citral and vitamin "A" on glaucoma.

In addition a number of films were shown.

P. D. Trevor-Roper
London

Classics of Ophthalmology
JAMES E. LEBENSOHN, Editor

THE EVOLUTION OF THE EYE

CHARLES DARWIN

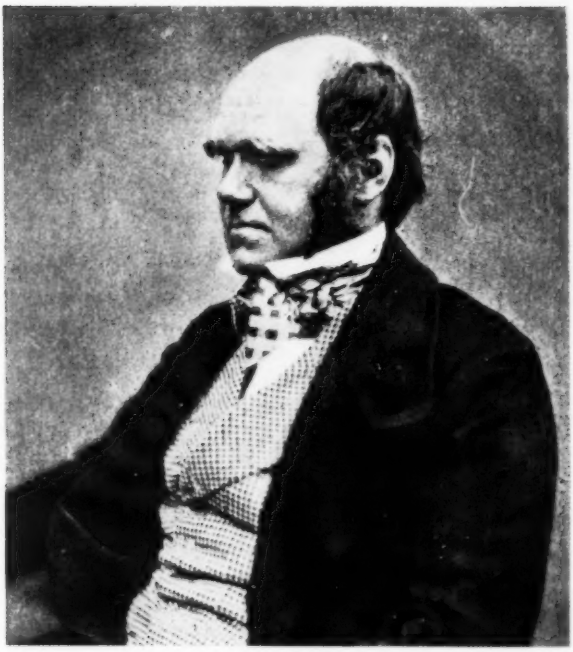
Down, England

Excerpt from *The Origin of Species*, Ch. VI, Ed. 1, 1859

To suppose that the eye with all its inimitable contrivances for adjusting the focus to different distances, for admitting different amounts of light, and for the correction of spherical and chromatic aberration, could have been formed by natural selection, seems, I freely confess, absurd in the highest degree. When it was first said that the sun stood still and the world turned round, the common sense of mankind declared the doctrine false; but the old saying of Vox populi, vox Dei, as every philosopher knows, cannot be trusted in science. Reason tells me, that if numerous gradations from a simple and imperfect eye to one complex and perfect can be shown to exist, each grade being useful to its possessor, as is certainly the case; if further, the eye ever varies and the variations be inherited, as is likewise certainly the case; and if such variations should be useful to any animal under changing conditions of life, then the difficulty of believing that a perfect and complex eye could be formed by natural selection, though insuperable by our imagination, should not be considered as subversive of the theory. How a nerve comes to be sensitive to light, hardly concerns us more than how life itself originated; but I may remark that, as some of the lowest organisms, in which nerves cannot be detected, are capable of perceiving light, it does not seem impossible that certain sensitive elements in their sarcode should become aggregated and developed into nerves, endowed with this special sensibility.

In searching for the gradations through which an organ in any species has been perfected, we ought to look exclusively to its lineal progenitors; but this is scarcely ever possible, and we are forced to look to other species and genera of the same group, that is to the collateral descendants from the same parent-form, in order to see what gradations are possible, and for the chance of some gradations having been transmitted in an unaltered or little altered condition. But the state of the same organ in distinct classes may incidentally throw light on the steps by which it has been perfected.

The simplest organ which can be called an eye consists of an optic nerve, surrounded by pigment-cells and covered by translucent skin, but without any lens or other refractive body.



CHARLES DARWIN
ABOUT 1854

In the great class of the Articulata, we may start from an optic nerve simply coated with pigment, the latter sometimes forming a sort of pupil, but destitute of a lens or other optical contrivance. With insects it is now known that the numerous facets on the cornea of their great compound eyes form true lenses, and that the cones include curiously modified nervous filaments.

When we reflect on these facts, here given much too briefly, with respect to the wide, diversified, and graduated range of structure in the eyes of the lower animals; and when we bear in mind how small the number of all living forms must be in comparison with those which have become extinct, the difficulty ceases to be very great in believing that natural selection may have converted the simple apparatus of an optic nerve, coated with pigment and invested by transparent membranae, into an optical instrument as perfect as is possessed by any member of the Articulate class.

He who will go thus far, ought not to hesitate to go one step further, if he finds on finishing this volume that large bodies of facts, otherwise inexplicable, can be explained by the theory of modification through natural selection; he ought to admit that a structure even as perfect as an eagle's eye might thus be formed, although in this case he does not know the transitional states. It has been objected that in order to modify the eye and still preserve it as a perfect

instrument, many changes would have to be effected simultaneously, which, it is assumed, could not be done through natural selection; but as I have attempted to show in my work on the variation of domestic animals, it is not necessary to suppose that the modifications were all simultaneous, if they were extremely slight and gradual. Different kinds of modification would, also, serve for the same general purpose: as Mr. Wallace has remarked, "If a lens has too short or too long a focus, it may be amended either by an alteration of curvature, or an alteration of density; if the curvature be irregular, and the rays do not converge to a point, then any increased regularity of curvature will be an improvement. So the contraction of the iris and the muscular movements of the eye are neither of them essential to vision, but only improvements which might have been added and perfected at any stage of the construction of the instrument." Within the highest division of the animal kingdom, namely, the Vertebrata, we can start from an eye so simple, that it consists, as in the lancelet, of a little sack of transparent skin, furnished with a nerve and lined with pigment, but destitute of any other apparatus. In fishes and reptiles, as Owen has remarked, "the range of gradations of dioptric structures is very great." It is a significant fact that even in man, according to the high authority of Virchow, the beautiful crystalline lens is formed in the embryo by an accumulation of epidermic cells, lying in a sack-like fold of the skin; and the vitreous body is formed from embryonic sub-cutaneous tissue. To arrive, however, at a just conclusion regarding the formation of the eye, with all its marvellous yet not absolutely perfect characters, it is indispensable that the reason should conquer the imagination; but I have felt the difficulty far too keenly to be surprised at others hesitating to extend the principle of natural selection to so startling a length.

It is scarcely possible to avoid comparing the eye with a telescope. We know that this instrument has been perfected by the long-continued efforts of the highest human intellects; and we naturally infer that the eye has been formed by a somewhat analogous process. But may not this inference be presumptuous? Have we any right to assume that the Creator works by intellectual powers like those of man? If we must compare the eye to an optical instrument, we ought in imagination to take a thick layer of transparent tissue, with spaces filled with fluid, and with a nerve sensitive to light beneath, and then suppose every part of this layer to be continually changing slowly in density, so as to separate into layers of different densities and thicknesses, placed at different distances from each other, and with the surfaces of each layer slowly changing in form. Further we must suppose that there is a power, represented by natural selection or the survival of the fittest, always intently watching each slight alteration in the transparent layers; and carefully preserving each which, under varied circumstances, in any way or in any degree, tends to produce a distincter image. We must suppose each new state of the instrument to be multiplied by the million; each to be preserved until a better one is produced, and then the old ones to be all destroyed. In living bodies, variation will cause the slight alterations, generation will multiply them almost infinitely, and natural selection will pick out with unerring skill each improvement. Let this process go on for millions

of years; and during each year on millions of individuals of many kinds; and may we not believe that a living optical instrument might thus be formed as superior to one of glass, as the works of the Creator are to those of man?

Comment: Darwin stressed that vision resulted from a continuous adaptive response to light and that any favorable mutation, however subtle and minute, gave its possessor a better chance for surviving the challenges of environment. The evolution of sight is no more wondrous than that of flight which progressed from gliding to annual distant migrations.

The simplest protozoa exhibits a surface photosensitivity that steers the organism to its optimum evironment. In the ameba this is attributed to a change in viscosity of its outer layer. The photomotor response increased in efficiency with the successive evolution of specialized light-sensitive cells in the anterior part of the organism, the addition of insulating and sensitizing pigments and of focusing devices to concentrate the light. In both plant and animal kingdoms the light-sensitizing pigment is derived from carotenoids. The derivative vitamin A systems, essential for image formation, are similar in eyes as widely diverse as those of man and the octopus.

In invertebrates, the retina, derived from the surface ectoderm, is connected secondarily to the nervous system. In vertebrates, however, the eyes arise from the neuroectoderm and a multi-layered retina assumes the function of the invertebrate optic ganglion. Though the vertebrate retina is always inverted and the invertebrate retina is usually erect, inverted retinas are seen in six of the spider's eight eyes and in the eyes of the scallop.

Ray Lankester (1880) suggested that the original pre-vertebrate eye was buried in the central nervous system as in the larval sea-squirt, a proto-chordate. He assumed that light traversed the transparent body and that as the body became more opaque with the progress of evolution, the eye travelled gradually to the surface. The transparent media of the eye retain the primitive transparency. The cornea, for example, resembles the integument of Amphioxus.

The neural tube had to come into being before the vertebrate retina could evolve. A suggestion of its incipiency is the median infundibular organ of Amphioxus, considered by Walls to be derived from photosensory ependyma. The rods and cones have been traced to the flagellae of ependymal cells, a conception that brings them in line with sensory hair cells in general. The course of evolution intimates that the cones are the older form since diurnality was the primitive status of Vertebrates. The lens, as shown by experimental embryology, is a secondary structure called forth by a chemotactic response to the developing optic cup. The semisolid vitreous first served to prop the lens in place, as the eye of the lamprey demonstrates. Diverse methods of effecting accommodation are illustrated in the fish, bird, horse and man. The fibrous and vascular coats of the eye are probably modifications of the meningeal envelops—dura mater and pia arachnoid respectively.

The pupil, fixed in lampreys and fishes, attains maximum motility in mammals. The rapid equalizing device of an active iris displaced the photomechanical changes of pigment migration used by the retinas of primitive forms. With evolution the acuity requirements steadily increase. Consequently in man the posterior segment becomes larger so that the visual cells are more numerous per angular unit of image, and the lens becomes flatter to be adapted for the greater focal distance. In the rabbit the depth of the vitreous chamber is less than the anterior-posterior diameter of the lens; in man it is about three times as great.

The ancestral vertebrates had a third eye, directed upwards. In fossil ostracoderms, a

socket for this eye is universally present, although much smaller than those for the paired eyes. Despite loss of function, the third eye persists, transformed into the pineal body.

The vexing problems of the ancestry of the Vertebrates and of the Primates have been clarified. The best clues to chordate origins are found in the Echinoderms. Their larvae, which exhibit bilateral symmetry, resemble the larval forms of proto-chordates; and unlike other invertebrates, the Echinoderms use creatine phosphate instead of arginine phosphate to spark the energy release for muscle activity. The earliest phase in the evolution of the Primates is represented approximately by the tree-shrew. In contrast to the true shrews, which are properly classified as Insectivores, the tree-shrew has a high visual development, stimulated undoubtedly by its arboreal life.

An outstanding feature of the evolution of the Primates is the progressive elaboration of the sense of vision. In the higher Primates the orbital apertures become directed forwards and stereoscopic vision is developed as a distinctive acquisition. The most marked trend in the evolution of man has been the special development of the brain. "Human vision is the product of a complex brain teamed with a relatively simple eye" (Walls).

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BIOGRAPHICAL NOTE

Charles Robert Darwin (1809–1882) was born on the same day as Abraham Lincoln, February 12, 1809. His father, a physician, had planned for Charles to follow his profession, but young Darwin found the medical teaching at Edinburgh uninspiring. Starting anew at Christ's College, Cambridge, he took his degree in 1831. Early in youth his scientific bent was stimulated by reading *The Natural History of Selborne* by Gilbert White—a classic in its field. At both Edinburgh and Cambridge he gained the friendship of the scientists there and worked with them at off hours. He spent the vacation after his commencement with Prof. Sedgwick, studying the geology of North Wales. On his return home he found a letter from Prof. Peacock of Cambridge inviting him to be the naturalist on H. M. S. Beagle in its surveying cruise around the world. When he left, on December 27, 1831, Darwin was 22 years old. He returned 5 years later with the finest collection of animals, plants and rocks ever assembled. At Galapagos, Darwin found seven distinct species of finches in the separate islands which he proved were all derived from a single species on the South American mainland. Though this and much other evidence convinced Darwin of the fact of evolution, the mechanism of evolution baffled him until in October 1838 he read Malthus on *Population* when the idea of natural selection flashed upon him. In 1839 he married his cousin, Emma Wedgwood, and in 1842 he finally published the journal of his voyage. In June 1858, A. R. Wallace, then in the Moluccas, sent Darwin a manuscript in which the theory of evolution and natural selection was independently developed. Darwin and Wallace presented their papers jointly before the Linnaean Society on July 1, 1958. Darwin's formal work *On the Origin of Species* was published on November 24, 1859, and the entire edition of 1250 copies was exhausted on the day of issue. During his last 40 years Darwin published 17 books, including the famous *Descent of Man* (1871). He is buried in Westminster Abbey; his home at Down, 20 miles from London, is now a museum.

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Book Reviews

"Atlas of the Ocular Fundus," by Oswald Marchesani and Hans Sautter, (*Translated by Philip*). *Hafner Publishing Co., New York, New York, $80.00,* 1959.

This atlas has been compiled from the selected material of two large hospitals. Dr. Sautter has arranged and added to the material left by his predecessor, Marchesani. Essentially he has confined himself to description of the characteristic appearances of the depicted diseases. Occasionally he has added further explanations when the existing material would permit and when it appeared especially important for instructional purposes. He has devoted more time to his own special scientific interests but has presented considerable description of all of the depicted fundus disorders. The book is intended primarily for the ophthalmologist, but it no doubt will be of considerable benefit to the general practitioner and specialists in other branches of medicine who take the time to peruse these beautiful illustrations.

The book is divided into seven sections starting with comparative ophthalmoloscopy showing the fundus of the guinea pig, rabbit, dog and chicken.

The normal fundus of the human eye is followed by the physiologic variants and malformations. There are illustrations of diseases of the optic nerve, the retina, the choroid and changes in the fundus due to trauma. Each illustration is accompanied by a description in English, French and Spanish. The English is done by Dr. Philip of Wales, the French by Professor Nordmann of Strasbourg and the Spanish by Dr. Lino of Buenos Aires. The illustrations, although slightly diagrammatic, are beautifully colored and quite instructive representing the reproductive artistic ability of Mr. Saumer and Mr. Zeltmann who are responsible for these many drawings. Several of the colored fundus photographs are accompanied by arteriograms, skull x-rays and pathologic specimens. The colobomas are accompanied by models of the entire globe which allow one to get a total picture of the coloboma. Particularly striking are the vascular occlusions involving branches of the central retinal artery and branch obstructions as well as total occlusion of the central retinal vein. One cannot help but admire the many beautiful illustrations in periphlebitis retina and of the various forms of diabetic retinopathy, pigmentary disturbances, angioid streaks and varieties of macular involvements which require no written description although a more than adequate one accompanies each illustration. The student who studies and familiarizes himself with these photographs will have no trouble in recognizing the clinical picture.

It is true that one's initial impression of the cost of this book could be very misleading for the many illustrations so beautifully reproduced make the cost seem like an exceedingly good investment. Certainly each teaching institution

should have one of these manuals available for its residents and staff. I believe the authors have made a considerable contribution to training in ophthalmology. There are actually 161 plates and 262 colored and 13 black and white illustrations. This is truly a beautiful as well as instructive presentation. There is no doubt that photographic reproduction of fundic lesions is a great step forward in ophthalmoscopy, but these beautiful and life-like illustrations reveal the tremendous value of well executed artistic interpretations.

IRVING H. LEOPOLD

"Rôle du système musculaire dans la pathogénèse et la thérapie du strabisme (Role of the muscular system in the pathogenesis and treatment of strabismus)," by Witold Starkiewicz, *Société des Sciences et des lettres de Szczecin; section des sciences médicales. Monographies, Vol. II, 1958, 133 pp.*

This is a translation into French of a monograph published in Polish and deals with the pathogenesis and treatment of strabismus. The author explains in detail the development of normal binocular vision in the child based on the establishment of conditional reflexes that involve the visual and tactile senses. The various muscles of the body are divided into those receiving impulses which will induce central visual localization, such as the muscles of the limbs, and those which by their tonicity will help localize the visual impulse. In the latter group belong the extraocular muscles, the cervical muscles and those rotating the trunk.

Aberrations in these localizing pathways result in strabismus. The treatment of squint consists in reeducating these localizing reflexes combining visual, kinesthetic and tactile impulses. Once the direction of the visual axis has been improved by surgery and the refractive error adequately corrected the first step of the localizing method consists in alternate occlusion for 1 to 4 weeks over a period of months up to one year. During that time the patient touches, grasps and moves different objects, approaches them to his eyes, head and body. In the second stage rapid, alternating occlusion is applied for 4 to 6 hours a day over 1 to 2 months. This is accomplished automatically by applying a small motor to the patient's forehead. An electric battery suspended in a bag on the patient's back supplies the current to the motor which changes the side of the occlusion every 1.5 seconds. In this fashion the child may play ping-pong or any other game requiring rapid motor reflexes, both eyes are obliged to work and normal connections between the two cerebral retinal projections are established. The author claims favorable results in 28 out of 36 children treated with this localizing method.

Unfortunately the poor quality of the translation renders the reading cumbersome and ambiguous. The basic concepts exposed are more or less acceptable, but some of the methods proposed to cure the squint would appeal to few ophthalmologists and even fewer patients.

H. E. CHODOS

"Neuro-ophtalmologie," by L. Giullamale, P. V. Morax and G. Offret, *Masson and Company, Paris. Plain binding $38.95; special binding $44.08.*

This two-volume work in French is an important contribution. It covers neuro-ophthalmology and its related basic sciences and specialties from a clinician's point of view and, as with its English counterparts, carries the weight of broad personal experience.

The format of the first volume is excellent, interweaving the anatomy and physiology along with the clinical affections in a systematic fashion through the visual pathways, pupils muscles, motor and sensory nerves, and pertinent elements of the central nervous system. The authors then discuss in separate chapters such subjects as nystagmus, the cephalgias, epilepsy, and psychovisual syndromes. The first volume ends with a well illustrated chapter of complimentary methods of diagnosis in neuro-ophthalmology. The latter is excellent since it illustrates very well the various radiologic techniques used to investigate intracranial pathology. As ophthalmologists we should be able to understand these radiologic techniques even though not called upon to give final decisions regarding their significant changes. In this volume the chapters on the visual pathways, pupils and sensory apparatus of the eye are complete, well written and illustrated. Reference notes and bibliography, other than that of the authors' own experience is unfortunately a deficit to many sections of both volumes. This is important since these are primarily reference books.

The second volume concerns more widely varied clinical subjects including congenital and hereditary disorders, trauma, and central nervous system infections. These are not well illustrated, a notable deficit in this volume especially. Treatment is neglected in these chapters also. This stands out particularly in the chapter on myasthenia gravis. The chapter on demyelinating diseases is well organized and quite complete. The section on optic neuritis is particularly helpful, since it reviews much of the authors' personal experience and reviews the statistics in the literature in various geographic locations giving clearly the incidence and wide variability as well as emphasis on the unknown factors in this common widespread disorder. Again treatment is not emphasized sufficiently. The chapter on circulatory disorders is adequate as regards our previous knowledge and yet emphasis on ophthalmodynamometry is conspicuously lacking here. These and other tools in the evaluation of our more current knowledge of the circulatory disorders leaves one with the impression that this chapter could be expanded and better illustrated. The brainstem syndromes are all included under vascular obstructions, and whereas it is true they are most commonly caused by them, this is not universally so and somewhat misleading.

The longest chapter concerns the broad subject of tumors of the optic nerve through the cerebrum into the brainstem. The chapter is well arranged, complete, and includes much fine material, from the experience of the authors.

The final chapter concerns complications of certain neurosurgical procedures. It is a valuable short summary of these dangers with which we should also be familiar since we are so often instrumental in subjecting patients to these hazards.

In summary, this two-volume text of 1,349 pages is well organized and written within an excellent format. It is a valuable contribution to our ever widening interest in this subject. The few criticisms considered valid are those pertaining to references, illustrations, and certain segments of the subject matter. They in no way detract from the value of these volumes to any and all interested in clinical neuro-ophthalmology, as well as its related basic sciences and specialties.

THOMAS R. HEDGES, JR.

Notices

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

Eastern Section Annual Meeting, Philadelphia, Pennsylvania

Thursday, February 18, 1960

PRESENTATION OF PAPERS

Cornea

9:20 A.M.—The Fine Structure of the Human Cornea
Marie A. Jakus, Ph.D., Retina Foundation, Massachusetts Eye and Ear Infirmary and Harvard University, Boston, Mass.

9:35 A.M.—Endocrine Factors and the Development of Corneal Transparency
Alfred J. Coulombre, Ph.D. and Jane L. Coulombre, B.S., Department of Anatomy, Yale University School of Medicine, New Haven, Conn.

9:50 A.M.—The Effect of Intralamellar Plastic Disks on Corneal Physiology
William A. Knowles, Wilmer Institute, Baltimore, Md.

Lens

10:05 A.M.—Further Investigation of the Organ Specificity of the Lens
W. Manski, Ph.D., T. Auerbach, M.A. and S. P. Halbert, M.D., Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, New York, N. Y.

10:20 A.M.—The Occurrence of Proteases in the Lens Active Under Acidic pH
Anima Devi, Ph.D., College of Physicians and Surgeons, Columbia University, New York, N. Y.

10:35 A.M.—Carbohydrate Metabolism in the Aging Rat Lens
Sidney Lerman, M.D. and Betty K. Ishida, B.A., University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

10:50 A.M.—Autoradiographic Localization of Tritium in Lens Epithelium
Clifford V. Harding, Ph.D. and B. D. Srinivasan, A.B., Department of Ophthalmology, Columbia University, New York, N. Y.

11:05 A.M.—Electron Microscope Observations on Human Senile Cataract
Theodor Wanko, M.D., Mary Ann Gavin, M.A., Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.

Uveitis

11:20 A.M.—Sensitivity Reactions to Tuberculin in the Eyes of Rabbits Passively Sensitized by Leukocytes
Mary M. Tremaine, Ph.D., University of New York Downstate Medical Center, Department of Microbiology and Immunology, Brooklyn, N. Y.

11:35 A.M.—Allergic Recurrences of Toxoplasmic Uveitis
Herbert Kaufman, M.D., Massachusetts Eye and Ear Infirmary, Boston, Mass.

11:50 A.M.—The Effects of Irradiation and Nitrogen Mustard on the Passive Arthus Reaction in the Rabbit Eye
Arthur F. Howe, Ph.D., Retina Foundation, Boston, Mass., and S. J. Bullington, M.D., Geisinger Memorial Hospital, Danville, Pa.

12:05 P.M.—A Study of Iridocyclitis Occurring in Rats with Arthritis Induced by the Injection of Freund's Adjuvant
S. J. Bullington, M.D., Retina Foundation, Massachusetts Eye and Ear Infirmary, Boston, Mass., Byron H. Waksman, M.D., Department of Bacteriology and Immunology, Harvard Medical School, Boston, Mass., Neurology Service, Massachusetts General Hospital, Boston, Mass.

12:20 P.M.—Lunch

1:30 P.M.—Osmotic Pressure Relationship—Plasma to Aqueous with Special Reference to the Elasmobranch Eye
Russell Doolittle and William Stone, Jr., M.D., Massachusetts Eye and Ear Infirmary, Ophthalmic Plastics Laboratory and Marine Biological Laboratory, Woods Hole, Mass.

1:45 P.M.—The Influence of Sanguinarine and Argemone Oil on the Intraocular Pressure of Cats, Rabbits and Chickens
G. C. Dobbie, M.D. and Maurice E. Langham, Ph.D., Institute of Ophthalmology, London, England

2:00 P.M.—Comparative Anatomy of the Ciliary Nerves
Patricia Grimes, B.A. and Ludwig von Sallmann, M.D., Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.

2:15 P.M.—Histochemical Localization of Cholinesterase in Human Extraocular Muscle
Carl Kupfer, A.B., M.D., Howe Laboratory, Harvard Medical School and Massachusetts Eye and Ear Infirmary, Boston, Mass.

2:30 P.M.—Experimental Diabetic Retinopathy
Andrew de Roetth, Jr., M.D., Med. D. Sc., Columbia University College of Physicians and Surgeons, New York, N. Y.

2:45 P.M.—Herpes Simplex Virus Inactivation by Chemical Agents
Theodore W. Sery, Ph.D., Wills Eye Hospital Department of

Research, Graduate School of Medicine, University of Pennsylvania, and Francis P. Furgiuele, M.D., Temple University, Philadelphia, Pa.

3:00 P.M.—The Distribution of Mast Cells in the Uvea
George K. Smelser, Ph.D. and Steven Silver, B.S., Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, New York, N. Y.

3:15 P.M.—A Study of Rod Activity at Photopic Intensity Levels
Joseph Mandelbaum, M.D., Med. Sc. D., New York State University, Brooklyn, N. Y., and Elliot Nelson, M.D.

3:30 P.M.—Distance Lateral Heterophoria and the Response ACA Ratio and their Relationship to the Elevation of the Plane of Regard
Henry A. Knoll, B.S., M.S., Ph.D., Bausch & Lomb Optical Company, Rochester, N. Y.

3:45 P.M.—The Influence of Retinal Adaptation Upon the Pupillary Reflex to Light in Normal Man
Otto Lowenstein, M.D. and Irene F. Loewenfeld, Ph.D., Columbia University College of Physicians and Surgeons, New York, N. Y.

Current Review

LAMELLAR KERATOPLASTY*

A Valuable Technique in Ophthalmic Surgery

J. Harry King, Jr., M.D., F.A.C.S.†

There are two well established methods of corneal transplantation, each having its own clearly defined indications. In blindness or diminished vision caused by corneal opacification or distortion, the penetrating (full thickness) technique is the most useful. For improvement of the structure and physiology of the cornea and to prevent corneal blindness, the lamellar (partial thickness) is preferred. This method is also indicated in cases of diminished vision if the corneal opacification is superficial.

PENETRATING KERATOPLASTY

Partial penetrating grafting is indicated in:

1. Corneal opacities or leukomata involving the deeper corneal layers.
2. Inactive interstitial keratitis.
3. Certain corneal dystrophies (Groenouw, early Fuch's).
4. Blood staining of the cornea.
5. Keratoconus, unless advanced.

The successful outcome of a penetrating corneal transplant is dramatic, but less than 10 per cent of those who are blind are candidates for this operation. It is a precise, time consuming, and expensive procedure, and although it may improve vision in 40 per cent of those operated upon for all indications, it may also result in lessened vision in 10 to 20 per cent or, in some instances, it may even result in loss of the eye.

With improvement in technique and instrumentation, complications during operation are less frequent, but the postoperative course is still fraught with such complications as delayed formation of the anterior chamber, dislocation of the graft, and iris herniation, all of which must be dealt with promptly. Delayed

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clouding of the graft is still a problem. This procedure, therefore, has limited use for the average ophthalmologist.

LAMELLAR (NONPENETRATING) KERATOPLASTY

This operation replaces one half or more of the corneal thickness without perforating through Descemet's membrane into the anterior chamber. It has wide application and includes aspects of corneal pathology which intimately concern every ophthalmologist. Whether or not he desires to perform the operation, he must recognize its values. It is a safer operation than penetrating grafting, although the technique is somewhat more difficult. It requires shorter periods of hospitalization and less disability for the patient.

According to Magitot[1] lamellar keratoplasty "can be used with success in 75 per cent of the cases where perforating keratoplasty is used today." Paufique[2] said it "has gained an honourable place in ophthalmic surgery" and Paton[3] stated it is "the most interesting development in keratoplasty and the least known in this country." Whereas a small percentage of eyes will be made worse following penetrating transplantation this would be a rarity after a lamellar graft.

The indications for lamellar transplantation are:

1. Optical
2. Preparatory (Tectonic)
3. Therapeutic
4. Cosmetic
5. Miscellaneous

Optical

Although the optical indications are numerous, lamellar grafting is indicated in fewer corneal conditions which cause marked reduction of vision, since improvement is not striking unless the opacification is confined to the superficial corneal layers. Visual results may be excellent in the following conditions:

1. Opacities or leukomas of the superficial layers.
2. Multiple foreign bodies in the anterior layers.
3. Band-shaped keratitis.
4. Dystrophies: Hereditary—Groenouw's (nodular), Haab-Dimmer (lattice), secondary (fatty).
5. Luetic and tuberculous keratitis, inactive.
6. Superficial rosaceous keratitis.
7. Recurrent pterygium.

Epithelial and *superficial stromal scarring* following repeated attacks of viral keratitis results in diminished vision. When the condition is quiet, with little or no vascularization, excellent optical results will follow a lamellar graft.

In opacification following keratitis from unknown etiology, if a small central clear area can be obtained, visual improvement follows lamellar grafting.

Groenouw's nodular dystrophy is ideally suited for a lamellar graft inasmuch as usually the inner corneal layers are uninvolved.

In the application of a lamellar graft for optical purposes, *inactive interstitial keratitis*, without vascularization, is similar to an old viral keratitis. If activity with vascularization is present, the indication for grafting will be listed as therapeutic as well as optical.

Pterygium with multiple recurrences and much superficial scarring in the visual axis is a candidate for lamellar grafting.

Preparatory

An important indication for lamellar grafting is its preparatory or tectonic use. It can be applied as a primary procedure to restore or improve the anatomy and physiology of the cornea in preparation for the penetrating graft which is performed later to improve vision.

In an unfavorable cornea, a lamellar graft can be used as a test for the success of a later penetrating graft. Paufique[4] has aptly stated that "if the lamellar graft loses its clarity, then the penetrating graft is sure to fail." Preparatory indications include:

1. Dense vascularized leukoma—chemical burns, injury, or disease.
2. Diffuse leukoma—uveitis, trachoma, etc.
3. Advanced keratoconus.
4. Active interstitial keratitis.

A penetrating graft is destined to failure if it is applied to a vascularized cornea or is used in the presence of certain active corneal disease. A *dense vascularized leukoma* is best treated first by a lamellar graft, and then by β-radiation to any newly forming vessels which are more sensitive than old vessels. If too much radiation is used before grafting, it may destroy the corneal nutrition. This is also true for *active interstitial keratitis*.

In *advanced keratoconus*, the cornea is often thinned beyond the cone well towards the corneal periphery. If a penetrating graft is applied which includes the cone but does not adjoin cornea of the same thickness, the graft may fail. Poor mechanical apposition of the posterior layers will result in hydration and opacification of the graft from the absorption of aqueous humor. If the cornea is thinned beyond a 7-mm. central radius, a lamellar graft is done to restore the cornea to its normal thickness in preparation for a later penetrating graft. In a number of our patients with severe keratoconus, a preliminary preparatory lamellar operation resulted in vision as adequate as would be expected from a penetrating graft, and the operations were considered final. If the central corneal scarring from previous hydrops is not extensive or is in the anterior layers, excellent optical results can be expected from a lamellar graft. The high irregular astigmatism in advanced conical cornea will be markedly reduced by a large lamellar graft. In performing *perforating* keratoplasty, it is important to include the entire cone; otherwise the cone may reappear at the graft's lower edge some years later. A large lamellar graft may give better long-term structural and visual results than a penetrating graft in severe keratoconus.

Therapeutic

The most valuable use of the lamellar graft is its application as a therapeutic procedure. It is very effective in treating progressive corneal disease or chronic and recurrent conditions of the cornea which do not respond to other methods of therapy. Paufique[4] stated that "therapeutic grafting is a primary indication for keratoplasty and is at least as useful as optical grafting (penetrating), if not more so. It actually amounts to a preventative treatment of corneal blindness." Franceschetti[5] feels that therapeutic grafting is used "to hinder the evolution of a corneal disorder." The therapeutic indications are numerous and include the following:

1. Recurring keratitis caused by a neurotropic virus (herpes simplex or zoster).
2. Progressive ulcerative keratitis.
3. Recalcitrant ulcers—Mooren's.
4. Interstitial keratitis, luetic or tubercular, active.
5. Recurrent keratitis of indefinite etiology.
6. Postoperative keratitis, dystrophic.
7. Recurrent "malignant" pterygium.
8. Corneal fistula.
9. To replace delimiting keratotomy.
10. Chemical burns.
11. Descemetocele.
12. Trophic effect for "disease" of a transplant.

Recurring active herpetic keratitis or *postherpetic keratitis*, including disciform and the metaherpetic type are indications for a lamellar graft.

Most dendritic herpetic corneal ulcers will heal following removal of the diseased epithelium. Some physicians feel that the diseased tissue should be treated with iodine, ether, or thermal cautery at the time of removal; others advise scraping the area with a platinum spatula and applying no cauterizing agent. at all. Gundersen prefers to wait for 24 to 48 hours until the dendritic pattern is well formed, but others think the earlier the affected epithelium is removed the better.

Herpes simplex corneal infections have increased in frequency and severity, and on this continent the condition is now the most important infectious disease of the eyes.[6] Stromal extension presents a serious complication and is estimated to occur in one out of three cases. Chronic stromal involvement (disciform) may be recurrent or it may remain active for months or years. When this is accompanied by recurrent superficial ulceration (metaherpetic), necrosis, of the stroma, followed by thinning, descemetocele, and perforation are apt to occur. There is no effective medical therapy for chronic viral keratitis. If the condition does not "burn out" in two or three months with supportive treatment, a therapeutic lamellar corneal transplant is advisable, and the graft must be large enough to include the entire area of diseased cornea. In most instances the cornea will heal promptly and the eye will become quiet. The true value of a graft under

these circumstances is unknown. In addition to removal of the diseased cornea containing the virus, the new healthy cornea may supply more fixed antibodies and may have a biologic or trophic effect.[7] Healthy cornea may contain some antivascular substance which is lost upon the death of the keratoblasts. Haziness of the cornea or of a graft is preceded by the penetration of vessels.[8] Best results are obtained when the graft is done early, before advanced neovascularization occurs.

The use of tarsorrhaphy or a conjunctival flap have also been advised for severe recurring or chronic keratitis which does not respond to medical therapy. In my opinion, there are very few, if any, indications for these procedures. If rupture of the cornea occurs and the facilities are not available for corneal grafting, a conjunctival flap will save the eye for future definitive surgery. A lamellar graft is preferable to a flap, and if a fresh donor cornea is not obtainable, a preserved cornea can be used. Preserved human corneas for emergency use will eventually be available in most eye banks. Every severe case of keratitis is accompanied by an active uveitis. If the pupil cannot be observed because of a flap, and if it cannot be kept mobile, dense synechiae may form. A cornea has been known to perforate under a thinned conjunctival flap.

An *ulcerative keratitis* which is progressing, or a *corneal abscess*, require an immediate graft following excision of the diseased corneal tissue well into healthy cornea. A serious ulcer, such as *Mooren's*, demands a graft when the diagnosis is certain.

Interstitial keratitis with active vascularization is best treated by a lamellar graft after and during an intensive course of corticosteroid therapy. The drug, together with antibiotic therapy, is given topically and systemically before the operation. β-Radiation is used for any vessels which reappear after grafting. In acute interstitial keratitis a graft during this phase will shorten the course of the disease by reducing vascular invasion and will decrease the amount of resulting corneal opacification.[8]

Recurrent keratitis—regardless of etiology, which results in repeated disability by causing pain, photophobia, and lacrimation—can often be cured by a lamellar graft.

A *dystrophic keratitis*, such as that which occasionally follows cataract extraction, is believed by many authorities to be an indication for a lamellar graft. Our results in these cases have been poor. Fuch's dystrophy usually involves the endothelium as well as the outer layers, and a penetrating graft is indicated in this condition. The disease often recurs in the graft and best results are obtained when the operation is done early, before extensive endothelial damage has occurred.

A highly vascularized, repeatedly *recurrent pterygium* can often be cured by excision and the use of a peripheral lamellar graft. This is a better procedure than the grafting of skin or mucous membrane at the limbus.[9]

A *corneal fistula* from trauma, a *perforated ulcer*, or a *ruptured descemetocele* are best repaired by a lamellar graft. It is usually impossible to properly apply a penetrating graft in the presence of a flat anterior chamber. If the surrounding

cornea is not diseased, a penetrating graft should be done if technically possible.

Delimiting keratotomy for keratitis or corneal ulcer is rarely required in this day of antibiotics. When it is indicated, however, it is now replaced by lamellar grafting.

Chemical burns of the cornea are an indication for a therapeutic graft, although authorities are not in agreement as to the time the graft should be done. Franceschetti and Maeder[10] make no distinction between an acid or alkali burn as far as gravity is concerned. They feel that a lamellar graft, for best results, should be performed as soon as possible, and Sourdille and Offret[8] emphasize that an immediate graft in a caustic burn will avoid deep penetration of the chemical. Berens[11] agrees with these opinions and recommends mucous membrane grafts surrounding the cornea when the conjunctiva and sclera are also damaged. This is though to improve the nutrition of the cornea. Paton[12] states that the eye may be saved by a lamellar graft in mild burns when the operation is done early. Castroviejo[13] does not believe in immediate grafting in burns but prefers conservative therapy until the eye is quieter. He feels that a lamellar graft should be delayed for at least one year.

The *tropic effect* of a lamellar graft was first emphasized by Filatov.[14] He applied small lamellar grafts near a clouding penetrating graft to influence clearing. Clarification of the surrounding diseased cornea is now recognized by all surgeons who perform grafting. Filatov attributed this trophic action as part of his theory of "biogenic stimulants." This, however, is not generally accepted. Regardless of the cause, the new corneal tissue exerts a clearing effect probably by improving the nutrition of the surrounding cornea.

Miscellaneous

In highly *nervous and mentally unstable* individuals, in the presence of *severe nystagmus*, and in some *one-eyed patients*, lamellar rather than penetrating keratoplasty is preferred. It is usually indicated in *children*, although in a very cooperative child the penetrating graft with appositional sutures can be used.

Aphakia, with vitreous in the anterior chamber usually demands the lamellar graft. If a penetrating graft is essential for optical purposes, it may be accomplished by using a "sword knife" and Bonaccolto rings to prevent loss of vitreous.

The results from *superficial keratectomy* are frequently unsatisfactory. The cornea remains thin, often irregular, and vascularization may be stimulated. The lamellar transplant leaves a regular surface and tends to clear the adjacent cornea.

DIAGNOSIS

Several diagnostic techniques are valuable in studying a cornea before lamellar grafting.

The hand battery Klein *keratoscope** is an aid in determining alterations in corneal curvature or in the surface smoothness. The instrument is held near the

* Keeler Optical Products, Inc., Philadelphia, Pennsylvania.

patient's eye and projects an illuminated placido disk which is viewed by the examiner through a magnifying lens in the central opening.

It is often useful to know the thickness of the cornea in instances of disease or degeneration before a graft is applied. This can be determined with the *pachometer*,* a measuring device with a scale graduated in 0.1 mm. which attaches to the arm of the Haag-Streit slit lamp.

Wood's black light, long wave ultraviolet, is valuable in determining the extent of involvement in viral keratitis, chemical burns of the cornea, vascularization, and other conditions. To my knowledge, its use in keratoconus has not been mentioned. The area of thinned cornea can be clearly outlined by using the black light and observing with the biomicroscope. The primary luminescent phenomenon is evident in early cases and is marked in advanced keratoconus. This is an aid not only in diagnosis but also in determining the size of the trephine to be used in keratoplasty.

TECHNIQUE

The *corneal trephine*† which is held steady by one hand and is turned from the side prevents wobbling and obtains a clear-cut graft.

An *operating microscope* is useful and is a necessity when dissection as deep as Descemet's membrane is required.

A *special clamp*‡ has been devised to hold an excised rehydrated preserved donor cornea while the graft is being dissected. When a fresh donor cornea is used, the Castroviejo electric keratotome is advantageous in excising the graft. Castroviejo has modified the base of our clamp by replacing the steel convex surface with a soft plastic surface so that the keratotome can be used with preserved donor corneas.

When the apex of the cone in keratoconus is extremely thin, or in the presence of a descemetocele, the entire host cornea around the area should be dissected, with the thin section being left until the last. Perforation can usually be prevented if care is exerted.

By eliminating cotton and gauze and using camel's hair or sable *brushes* for swabbing, cotton fibers and lint are prevented from becoming embedded in the graft interface.

The *fine virgin silk sutures* of Barraquer are an advance in all corneal surgery. They are strong and cause very little trauma. Sutures should be inserted near the edge of the graft and then farther into the recipient cornea. If fluorescein stain is applied at the time of suture removal (18 to 21 days), the sutures are more readily seen. The use of a piece of razor blade held with the European clamp handle is an excellent knife for suture removal. The suture does not have to be held by forceps but is gently touched by the very sharp blade and is then removed by toothless forceps.

Following the use of a large lamellar graft, the eye must be kept *soft* for

* Stercks-Martin Limited Optical Co., London, England.

† Corneal trephine, King, manufactured by Storz Instrument Co., Saint Louis, Missouri.

‡ Furness Clamp, manufactured by Storz Instrument Co., Saint Louis, Missouri.

several days to help the graft maintain its proper position. A paracentesis can be done. The administration of 500 mg. of Diamox, intravenously, at the termination of the operation, a firm pressure dressing, and Diamox, orally, for the first week are advisable.

Tranquilizers, such as Trilafon, make the postoperative course easier for the patient.

In summary, the many uses of lamellar keratoplasty have been reviewed. It "has gained an honourable place in ophthalmic surgery"[2] and is a valuable technique which deserves consideration by every ocular surgeon.

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Special Article

CATARACT FORMATION IN HUMAN AND EXPERIMENTAL DIABETES

PART I

JOEL B. CHODOS, M.D., AND HEDWIGE E. HABEGGER-CHODOS, M.D.

Wills Eye Hospital and Graduate School of Medicine, University of Pennsylvania, Philadelphia

I. Introduction.
II. Histology of normal lens.
III. Metabolism of lens.
A. Carbohydrate metabolism.
1. Embden-Meyerhof cycle.
2. Oxygen utilization and citric acid cycle.
3. Permeability of lens.
B. Protein metabolism.
IV. Symptomatology of diabetic lens.
A. Refractive changes.
V. Morphology of diabetic cataract.
A. Pathologic histology.
B. Biomicroscopy.
C. Clinical picture.
VI. Incidence of diabetic cataract.
VII. Genetic aspects of diabetic cataract.
VIII. Experimental diabetic cataract.
IX. Pathogenesis of diabetic cataract in man.
X. References.

INTRODUCTION

"So many articles have already been written on the subject of the crystalline lens, that an attempt to add to their number seems to demand an apology." Thus Dorothy Rose Adams expressed herself at the beginning of her review of the literature on the lens about 34 years ago. And yet to this very day, the intimate functions of the lens which is useful only as long as it remains transparent, are still a mystery to us.

The Egyptians observed cataract formation around 3500 B.C. and diabetes

was recognized in antiquity by Hindu physicians (Gordon, 1949). However, the two diseases were not to be associated with each other for an almost unbelievable length of time. Rollo in 1798 was the first to observe the appearance of cataracts in diabetics as a distinct clinical entity and his patients were treated with a high protein diet. He felt that the association of cataract and diabetes in the same patient was fortuitous. Jahn (1834), Berndt (1834), Unger (1836), Benedikt (1842), and Himly (1843), were among the first to relate the two affections. By 1854, Mackenzie had already collected a series of cases with diabetic cataract. In 1873, Leber reported that the diabetic lens contained sugar, while in England, France (1859) observed "that the ocular affection arises only after a considerable duration of the renal malady." Becker (1877) classified the cataract in the older diabetic as a mixed cataract. In 1883 he firmly established the diabetic cataract as a clinical entity and described the soft cataract of the young diabetic becoming round in its capsule as the result of an excess of fluid beneath the anterior and posterior capsules; first the equatorial zone becomes opaque, then the posterior and anterior cortex. Förster (1877) considered certain superficial and nuclear lens changes typical of diabetes and on several occasions was able to predict the presence of sugar in the urine by observing the lens. The same author was of the opinion that the aqueous humor exerted a definite influence on the lens and his observation that lens changes in the young diabetic were bilateral was destined to be confirmed by succeeding generations.

Thus, the knowledge acquired during the 19th century was the beginning of the many investigations which were to follow. The elucidation of the pathogenesis of senile cataract formation in apparently healthy individuals of the older age groups is a difficult problem as usually only cataractous lens, the end point of the process, can be obtained for study. On the other hand, it is not practical to maintain laboratory animals in the hope that they might develop spontaneous senile cataracts, making it possible to analyze different stages in the evolution of the process.

Attention of observers was then focused on the production of cataract in experimental animals realized in days or months. The experimental diabetic cataract became notoriously popular after the discovery of alloxan. With the advent of the slit lamp in the early 1920's precise observations of rapidly developing human cataracts, mostly in young diabetics, became possible. These clinical and experimental observations stimulated biochemical and histologic observations of the lens under various conditions, and the information amassed was to be related to senile cataract and interpreted in the light of what was happening in the rest of the human organism.

However, the physiology, biochemistry and histology of the lens had to be understood before any comparison could be made with pathologic processes and rabbits or cattle provided a ready source of normal material for the laboratory.

HISTOLOGY OF THE LENS

The lens is an avascular organ; it gains nourishment mostly from the aqueous humor in which it bathes, and partly from the vitreous body lying posteriorly.

Embryologically, the lens is of ectodermal origin and is a simple organ, enclosed in a capsule with a single layer of epithelial cells on the anterior surface. These cells are flatter in the polar regions and become elongated towards the equator, where on saggital section they will be seen to rotate about an antero-posterior axis, taking up an oblique position. This is the germinative zone. In the region of the equator, some of the epithelial cells become elongated, their nuclei assume an oval shape and they are transformed little by little into lens fibers. The first elements to become fibers advance behind the other epithelial cells and extend at the same time underneath the posterior capsule. The superficial fibers of the lens are being continuously displaced from the periphery towards the center of the lens by apposition of new layers of fibers.

The young and active layers of the lens are therefore superficial and constitute the cortex. During their migration the lens fibers become older with an increased index of refraction, and make up the central nucleus. Thus, in any given layer of the lens, the fibers will all be of the same age. Nuclei become rarer in the deeper layers of the lens. A lipid membrane enclosing the young fibers can be made evident with a heavy metal stain (Friedenwald and Small, 1931). An albuminous liquor in the interior of the superficial fibers escapes when the fiber is no longer intact (Nordmann, 1954). The deep fibers never enclose any of this liquid. As a result of aging the lens nucleus becomes sclerotic, whereas the epithelium undergoes only slight changes. Thus, for the purpose of our exposé we can consider the anatomy of the lens in a simplified fashion as consisting from without inwards of a capsule and epithelium, superficial cortex underneath the epithelium, deep cortex and nucleus. The germinative zone previously mentioned is also of considerable importance.

These different parts of the lens will be seen to have different biochemical functions in the metabolic make-up of the lens and vary in their susceptibility to noxious agents.

METABOLISM OF THE LENS

A. Carbohydrate Metabolism

The lens requires energy for a variety of purposes. The growth of the lens is continuous and the cells of the lens multiply up to the most advanced age. In addition, the transparency of the lens must be maintained involving a physico-chemical state of balance between Na and K ions. Kleifeld (1953) and Kleifeld *et al.* (1953) demonstrated the active participation of the lens fiber in accomodation. The vitally important protein metabolism of the lens concerning synthesis, transformation and catabolism as well as active transfer of metabolites across the capsule and cell membrane requires energy. The source of this energy is from the catabolism of carbohydrate. The lens can in fact metabolize glucose under aerobic or anaerobic conditions as shown by Kronfeld and Bothman (1928) and later by Morone and Citroni (1950).

1. Embden-Meyerhof Cycle. The lens utilizes the glucose of the surrounding milieu (Kronfeld and Bothman, 1928; Cohen and Killian, 1929). Glycolysis in the lens presents many analogies with glycolysis in muscle and the first step in

either mechanism is a phosphorylation of glucose (Süllmann, 1937). The lens *in vitro* forms phosphoric esters of the carbohydrates, and this capacity diminishes with age, but is retained in cell-free extracts (Süllmann, 1937). The final degradation product of hexose-phosphate is lactic acid and this process is vigorously activated by the addition of phosphate as well as hexokinase (Weekers and Süllmann, 1938). Fischer in 1931 observed that in the aphakic eye the aqueous humor contained less lactic acid than the normal eye.

Von Euler *et al.* (1938 and 1939) as a result of their experimental work concluded that all the enzymes necessary for the anaerobic breakdown of carbohydrates were found in the lens. In 1953 van Heyningen and Pirie demonstrated hexokinase in the lenses of calves, the enzyme responsible for the initial phosphorylation of glucose. Nordmann *et al.* (1954*a*) verified by refined techniques the presence in the lens of the various enzymes required for glycolysis. Thus, it was established that the lens derived at least part of its energy from the anaerobic breakdown of sugars. Green *et al.* (1955*a*, *b*), confirmed this opinion by showing that the Embden-Meyerhof scheme operated in the lens.

2. Oxygen Utilization and Citric Acid Cycle. The aqueous humor is the source of oxygen for the lens and de Haan (1922) showed that the oxygen tension in the aqueous humor of rabbits is the same as that of venous blood. The oxygen requirements of the lens are small but a measurable amount is consumed, as can be seen in the difference of oxygen tension between the posterior and anterior chamber (Friedenwald and Pierce, 1933). The over-all consumption of oxygen by the lens is very low, but if it is understood that the nucleus of the lens does not utilize any oxygen, then the QO_2 (cu. mm. of oxygen consumed per mg. of dry weight of tissue per hr.) of the lens compares favorably with other organs (Frohman and Kinsey, 1952). The cytochrome system intervenes in the cellular respiration of the lens and can be inhibited with cyanide which causes a 91 per cent reduction in oxygen consumption (Ely and Robbie, 1950). The cytochromes are hemic proteids containing heavy metals. Herrmann and Moses (1945) implied the presence of cytochrome *c* and cytochrome oxidase in the lens epithelium. Christiansen and Leinfelder (1952) affirmed that the enzymatic character of lens respiration did not take place, as boiled lens consumed oxygen. However, Nordmann *et al.* (1954*b*) proved that any utilization of oxygen by boiled lens was due to an auto-oxidation of protein denatured by the boiling. In addition, Harris, Hauschildt and Nordquist (1953) showed that the refrigerated lens reverses the cation shift, that is, re-establishes a normal Na:K ratio more readily in the presence of oxygen than in its absence.

In 1927, Ahlgren demonstrated the presence of citric acid dehydrogenase in the lens. Grönvall (1937) showed citric acid to be a normal constituent of the aqueous humor in the pig and rabbit. In 1937, Krause described the probable pathways for the anaerobic and aerobic breakdown of carbohydrates in the lens. Krause and Stack (1939) determined the citric and malic acid content of the various ocular tissues. Von Euler *et al.* (1939) investigated the respiratory system of the lens and found it to be incomplete. These investigators could not demonstrate the presence of cytochrome or cytochrome oxidase but found the lens to

be rich in cozymase and codehydrase II. The lens was apparently able to synthesize ascorbic acid.

These observations suggested that the citric acid cycle might be operative in the lens. The oxidative enzymes necessary for the functioning of this cycle were demonstrated by Kinsey and Frohman in 1951. Merriam and Kinsey's results (1950*b*) showed that some of the glucose used by the lens did not appear as lactic acid and was presumably oxidized. In 1951 Ely found that bovine lens homogenates were capable of oxidizing lactic, pyruvic, oxaloacetic, citric, α-ketoglutaric and malic acids. The addition of cytochrome *c* was essential for the maximal aerobic oxidation of α-ketoglutarate by the bovine lens homogenates.

We may assume that the lens makes use of the citric acid cycle as Achard (1953) discovered that malonate and fluoracetic acid, which are known to inhibit the citric acid cycle, cause a notable reduction of the ATP content of the lens. Müller *et al.* (1956) in their review of the phosphate metabolism of the lens emphasized that the citric acid cycle is an excellent source of energy, the catabolism of 1 molecule of pyruvic acid resulting in the formation of 15 molecules of adenosine triphosphate (ATP).

Kinsey and Frohman (1951) pointed out that not all parts of the lens are able to oxidize carbohydrates, as the necessary oxidative enzyme systems are found only in the epithelium of the lens. Thus, any compounds containing high energy phosphate formed by oxidative metabolism presumably would be produced in the lens epithelium. In fact Kinsey and Frohman found the concentration of utilizable high-energy phosphate highest in the lens epithelium, varying inversely throughout the cortex with the distance from the epithelium, and immeasurably small in the nucleus. The relatively high concentration of compounds containing the high energy phosphate bond in the epithelium supports the hypothesis that this structure contributes energy for the metabolic requirements of the whole lens. The authors' results lead to the conclusion that the oxidation of carbohydrate in the epithelium is strictly aerobic, while that of the cortex and nucleus is strictly anaerobic.

The lens epithelium in fact absorbs radioactive phosphorus to a concentration 100 times that of the rest of the lens (Havener and Knorpp, 1954).

Kinoshita (1955) found oxygen essential to the viability of the lens, but his studies with radioactive carbon indicated that the citric acid cycle is relatively inactive in the lens. The possibility that a glutathione-ascorbic acid oxidative mechanism exists in the lens in place of the cytochrome system was advanced. The reaction would involve the oxidation of reduced triphosphopyridine (TPNH) by oxidized glutathione and catalyzed by glutathione reductase as shown by van Heyningen and Pirie (1953).

The multitude of oxidation-reduction systems found, in addition to the respiratory chain system in the lens, such as glutathione, cysteine and ascorbic acid may be of great importance as there is a possibility that they are linked with the cytochrome system. These oxidation-reduction systems have often been interpreted as being an oxidation-reduction reserve for the cytochrome system (Müller *et al.* 1956). Wortman and Becker (1956) on investigating the various enzyme

activities of the glycolytic and citric acid cycle, as well as that of the hexose-monophosphate shunt, suggested that the latter alternate route of oxidative carbohydrate metabolism was of lesser significance in the lens.

Thus, we have briefly reviewed the highlights of carbohydrate metabolism in lens, showing that the lens derives energy from the aerobic and anaerobic breakdown of glucose supplied to it by the aqueous humor. The importance of the various mechanisms of carbohydrate degradation available to the lens is difficult to estimate, but it is certain that glycolytic catabolism itself cannot provide all the necessary energy requirements. It would seem highly probable that the high energy phosphate compounds formed in sufficient quantities in the epithelium diffuse into the inner strata of the lens as suggested by Kinsey and Frohman.

3. Permeability of Lens. Another point to consider is the permeability of the lens capsule to the various sugars and electrolytes. The permeability of the capsule decreases with increasing molecular weight of the substance. The penetration of glucose into the lens according to Müller (1939) and Harris, Hauschildt and Nordquist (1955) is dependent not only on a simple process of diffusion resulting from relative concentration but also on enzymatically controlled phosphorylations. Galactose undergoes phosphorylation with some difficulty and penetrates slowly into the lens (Weekers, 1939). The lens can also form the phosphoric esters of fructose and mannose (Süllmann, 1937).

Müller (1939) and Müller and Kleifeld (1953) showed that iodoacetate inhibited the penetration of glucose into the lens *in vitro*. Sodium iodoacetate is known to inhibit phosphorylative processes. It probably does not act by inhibiting the hexokinase reaction, but by inhibiting the metabolic processes which result in the formation of the high-energy bonds of adenosine triphosphate (Pirie and van Heyningen, 1956). The presence of insulin in the incubating medium does not seem to influence either the penetration or the utilization of glucose by the rabbits' lens *in vitro* (Harris, Hauschildt and Nordquist, 1955). Glycogen has never been found in the lens.

B. Protein Metabolism

Little is known of the protein metabolism in the lens. It has been shown that C^{14}-labeled glycine is taken up by the cultured rabbit lens at a rate corresponding to a replacement of approximately 2.5 to 5 per cent of the protein glycine a day (Merriam and Kinsey, 1950*a*).

The amount of glycine incorporated in 24 hours into the protein of the anterior cortex and posterior cortex was respectively 5 and 2.5 times that incorporated into the nucleus. In other words, the parts of the lens rich in ATP and ADP took up more of the tagged amino acid.

Kinsey and Merriam (1950) calculated that the rate of turnover of glycine in lens glutathione was 2.35 per cent per hour. The same authors have shown that the lens nucleus is not dead in the metabolic sense, since protein synthesis as indicated by isotopically labeled glycine uptake is measurably present in the lens nucleus. The non-nucleated cells of lens fibers in the nucleus still contain enzymes. The concentration of lactate is higher in the nucleus than in the epithelium where

an excess of pyruvate is found, attesting to the different modes of glucose breakdown in various segments of the lens. In 1957, Nordmann emphasized the importance of protein metabolism in lens physiology. The lens can oxidize several amino acids to keto-acids (de Vincentiis and Aurichio, 1950).

Lenses of cattle and rabbits are capable of oxidizing certain fatty acids (de Leonibus, 1941) and even more so their ethylic or methylic esters. As far as it is known, the lens metabolizes fats in the same manner as other tissues.

SYMPTOMATOLOGY OF DIABETIC LENS

A. Refractive Changes

The patient's subjective complaints during the course of his disease (Desmarres, 1858), such as variable refractive and accommodative changes, reveal the primary alterations in the lens which could continue to opacification if the patient were left untreated (Cohn, 1878; Neuberger, 1903). There are two schools of thought concerning the explanation of these refractive changes. The first group invokes extralenticular causes, while the second advocates purely lenticular phenomena as being responsible for these symptoms. Alaerts and Slosse (1957) suggest in addition a paralysis of the ciliary muscle.

The refractive changes may be in the form of a myopia, hypermetropia or astigmatism, and are always bilateral. The symptoms appear suddenly during periods of deterioration of the general state of health. Myopia is observed with aggravation of the diabetes, (Alexander, 1903; Appenzeller, 1896; Berke, 1933; Bouchardat, 1852; van der Brugh, 1901; Burch, 1928; Castrignani, 1935; Duke-Elder, 1925; Gould, 1907; Grafe, 1924; Greeves, 1932; Griesinger, 1860; Grimsdale, 1899; Grönholm, 1918; Hirschberg, 1890; Mialhe, 1849; Milkie, 1956; Risley, 1897; Schapringer, 1893; Schieck, 1907; Terrien, 1921; Turtz and Turtz, 1958; Vogt, 1931; Weeks, 1906), whereas hypermetropia accompanies periods of amelioration (Ballantyne, 1925; Betsch, 1931; Bücklers, 1939; Davis, 1912; Doyne, 1899; Dykman, 1926; Enroth, 1918, 1920; Fischer, 1934; Gallus, 1906; Gifford, 1928; Granström, 1933; Hagen, 1921; Hermans, 1954; Horner, 1873; Knapp, 1909; Landolt, 1887; Lichtenstein, 1906; Lundsgaard, 1907, 1910, 1919*a*, *b*; McGrath, 1933; Maxwell, 1931; Moore, 1888; Odeneal, 1930; Pöllot, 1920; M. H. Post, 1917; L. Post, 1926; Risley, 1897; Roberts, 1920 and 1923; Rönne, 1915; M. Rosenstein, 1924; S. Rosenstein, 1858; Skwirsky, 1955; Wölfflin, 1911; Zentmayer, 1912).

Bidault and Ledoux (1957) described an exception to this rule. In one of their patients, the authors noted a hypermetropia in relation to increasing blood sugar levels and poor control, whereas with amelioration the hypermetropia disappeared. Furthermore, this patient presented with slight symptoms of myxedema and pituitary insufficiency. However, the fact remains that if myopia is present, it will precede the hypermetropia. Layton and Olmsted (1948) observed hypermetropia in alloxan-diabetic dogs with progressive hyperglycemia. The hypermetropia always follows the myopia, whereas the reverse is never observed. The refractive changes are not influenced by the instillation of atropine. The incidence of these symptoms and their extent vary with the different authors.

Nordmann (1954) noted 200 cases of refractive diabetic changes described in the literature. Granström (1933, 1937) found 71 per cent of his diabetics with refractive changes, whereas Obal in 1950 described 66 cases of sudden myopia in 168 young diabetics during the period of lack of insulin and proper diet in Berlin during 1947. Alaerts and Slosse (1957) believe that the percentage of cases compared to the total number of diabetics is minimal, and that the refractive changes are usually small, about 1 or 2 diopters. Granström (1933), Attiah (1948), Kumm *et al.* (1950) all agree that this symptom is seen mainly in the young diabetic, which leads one to believe that if the refractive change is of intralenticular origin it would occur more readily in the young lens. The characteristic feature of this refractive change in the diabetic is its sudden onset. An inexplicable myopia appearing rapidly in a young individual may be symptomatic of diabetes, (Bercioux, 1932; Kako, 1903; Hagedorn, 1922; Himsworth, 1932; Larsen, 1927; Rudy and Sachs, 1935), whereas in the known diabetic it is a danger signal (Berke, 1933; Cordes, 1952). The duration of this symptom is variable, and Granström (1933) observed a case lasting for 40 days whereas the shortest duration would be 11 days, with the exception of one observed case lasting for only 1 hour (Granström, 1937).

These variations in refraction are of interest to us as they may be indicative of the very first changes taking place in the lens. It is only in the beginning processes of lens alterations that we can hope to discover the sequence of events leading to the final cataract. The various types of total cataract resemble each other to a very remarkable degree, as the changes they show are mostly secondary.

The extralenticular changes which may be taken into consideration as giving rise to these refractive changes are accommodative spasm, paralysis of the ciliary muscles (Hudelo, 1930; Geiger and Roth, 1932; Badot, 1933; Blanchi, 1947), or a physico-chemical alteration of the intraocular fluids, that is, the aqueous or vitreous humor. There are serious objections to accommodative spasm, as spasm is never seen in diabetics, and furthermore, the instillation of atropine to paralyze the ciliary muscle does not alter the refractive changes (Lundsgaard, 1907; Rosenstein, 1924). Huggert (1954*a*) found paralysis of accommodation frequent in diabetics. The concentration of glucose in the aqueous humor necessary to produce refractive changes of even 2 diopters would be incompatible with the continued transparency of the lens (Hudelo, 1930; Duke-Elder, 1925). Huggert (1954*b*) observed an anterior displacement of the lens in one of his cases, but this etiology has not received popular support. Enroth (1920) noted the nucleus becoming hazy during the phase of hypermetropia and later appeared clear. Alaerts and Slosse (1957) maintained the old theory of Hudelo (1930) and consider the ciliary muscle as consisting of two parts, that is, fibers disposed in a radial and circular fashion. The circular fibers are constrictive and innervated by branches of the third cranial nerve, whereas the radial fibers are supplied by nerve endings of the sympathetic nervous system. Atropine paralyzes the muscle of Müller (circular fibers) resulting in an exaggerated traction of the antagonistic radial fibers and a diminution in refraction. Eserine induces a spasm of the ciliary sphincter and thus augments the refraction. Thus, if both the circular and radial

fibers were paralyzed due to some hypothetical diabetic toxin, an increase in refraction of the lens and a myopia could be explained (Mehlhose, 1949). If we were to suppose that the radial fibers recuperated more readily from the paralysis then an exaggerated traction from these fibers would result in a hypermetropia exceeding the normal physiologic state. Alaerts and Slosse propose this explanation to complete the intralenticular theories of Duke-Elder and Weekers. Duke-Elder feels that as a result of the hyperglycemia the blood stream is diluted by water from the tissues, creating a hypotonic aqueous humor and imbibition of water by the lens, thus augmenting the refraction of the lens with a resulting myopia. The opposite occurs during amelioration of the diabetes. Weekers (1941) believes that the refractive changes are due to alterations in the refractive index, all this representing the first and reversible stages of an impending cataract (Neuberger, 1903).

The theory of Duke-Elder is subject to several criticisms mainly that a hyperglycemia of a definite degree does not in all cases cause these refractive changes. Weekers (1941) administered galactose and created a hypertonic aqueous humor which also resulted in a myopia and some opacification of the lens. He never observed a hypermetropia under these circumstances.

Elschnig (1923) described the case of a diabetic with unilateral aphakia. A myopia of two diopters was noted which disappeared with amelioration of the diabetes, but no change in refraction occurred in the aphakic eye. However, Legroux (1952) reported refractive changes in the aphakic eye of a diabetic patient.

MORPHOLOGY OF DIABETIC CATARACT

A. Pathologic Histology

Though excellent descriptions of cataracta diabetica in man were available from distinguished authors, ophthalmologists and pathologists (His, 1854; von Graefe, 1858; Knapp, 1863; Becker, 1877, 1883; Förster, 1877; Kamocki, 1887, 1892; Görlitz, 1894; Hess, 1904, 1911), they were outmoded with the advent of the slit lamp. The observations *in vivo* of the dynamic processes within the lens of diabetic patients completed the histopathologic picture. His (1854), among the first to record the postmortem lenticular changes in a diabetic patient, found segmentation of the lens fibers and "fatty droplets" without any membrane. Knapp (1863) observed a granulated aspect of the epithelial cells the nuclei of which were swollen, as well as an alignment of small round-shaped figures (vacuoles?) between the lens fibers. No mention of the capsule nor the superficial cortical layers was made, as the lens extraction in that case had been extracapsular.

Becker (1883) insisted on the edematous, round appearance of the cataracta mollis juvenum. The edema dissociated the lens fibers so that the capsule adhered to the rest of the lens only in the equatorial area. Near the anterior pole the epithelium showed proliferation. Becker noted also the presence of vacuoles in the equatorial area, whereas punctiform opacities appeared only in the peripheral fibers under the capsule. Becker concluded that "the hydrops capsulae

lentis" occurring *in vivo* explained the clinical aspect of the diabetic lens. Several authors (Kamocki, 1887; Deutschmann, 1877, 1879, 1886; Groenow, 1904; Kako, 1903; Pichler, 1901) confirmed Becker's findings. Kamocki (1892) emphasized that the hydrops also involved the pigment epithelium of the iris.

B. Biomicroscopy

In 1923, Schnyder, the assistant to Professor Vogt, provided us with an excellent observation of the biomicroscopic picture of the diabetic cataract. This description has remained a prototype and was adopted by Vogt in his atlas of biomicroscopy of the lens.

Schnyder's patient was a 33-year-old woman with diabetic symptoms for 2 years and ocular disturbance for 5 months, with an average glycemia of 272 mg. per 100 ml. Bilaterally, the sagittal diameter of the lens was found to be diminished. This point was confirmed by Vogt not only for the diabetic but also as regards the lens in tetany. The bands of dysjunction were not clearly defined, and the surface of the embryonic nucleus appeared hazy. The cataract was formed of very numerous punctiform, dust-like, gray opacities, lying almost entirely under the capsule anteriorly and posteriorly. They were arranged in groups varying in size from 0.04 to 0.10 mm. and some appeared like droplets. A few irridescent bodies could be seen. Only rare opacities were found in the superficial layer of the cortex. One year later Schnyder was able to add new details to his original description. With deterioration of the diabetic condition, subcapsular vacuoles appeared as well as grayish, punctiform opacities along the suture lines. The structure of the lens fibers became more accentuated and clear clefts occurred in between (Wasserspalten). Later confluence of the vacuoles made the lens appear as if pierced with tiny holes and tumescent, while the depth of the anterior chamber decreased. This phenomenon has been described as early as 1859 by France: "The lenses have increased remarkably in their anterior-posterior diameter so as to encroach upon the depth of the anterior chamber and even to interfere mechanically with the free play of the iris. The opacity has attacked portions of several strata of the crystalline at once, leaving intermediate spaces for a while transparent."

The change in the dysjunction bands of the lens is an early sign of juvenile diabetic cataract (Huggert, 1953). Further evidence was gathered by Janert *et al.* (1956) who also considered the increased density of the peripheral sutures as precursors of diabetic cataract. The opacities described by Schnyder (1923) as dust-like and punctiform, and the larger ones as cloud-like have been compared by other observers to flocculi or snowflakes, hence the name of snowstorm cataract (Badot, 1933; O'Brien, Molsberry and Allen, 1934; Kumm, Mehlhose and Obal, 1950). In some cases iridescent crystals are found in the flocculi (Nobécourt and Ducas, 1933). The subcapsular opacities are typical not only of diabetic cataract and may be seen in other types of cataract (Anderson, 1924; O'Brien, Molsberry and Allen, 1934; Moore, 1936; Nordmann, 1954). In general the posterior subcapsular area is first invaded by the opacities rather than the anterior. In some cases the posterior flocculi become confluent under the capsule to form

a saucer-shaped opacity (Jany, 1879; Nobécourt and Ducas, 1933; Marr, 1952). Though classically the opacities remain in the superficial layers of the lens, cases have been reported in which the whole lens was invaded by them (Bangerter, 1938, Nobécourt and Ducas, 1933). This latter type of lenticular changes is believed to occur in the slowly progressive cataract (Bangerter, 1938), whereas the form described by Schnyder (1923, 1924, 1929), Alajmo (1927), Goulden (1928), and Sourasky (1929) is found in the rapidly tumescent form.

C. Clinical Picture

The main clinical features of the typical diabetic cataract are its rapid, bilateral development in a young diabetic under poor control. These points were summarized by Lecorché in 1861 in these words: "Sa fréquence, sa marche et son développement la caractérisent parfaitement et permettent d'en faire une individualité morbide bien définie. Elle est molle ou demi-molle. Elle ne se rencontre pas dans les cas de diabète léger qu'on peut facilement enrayer. Elle appartient à la symtomatologie du diabète grave." Probably the youngest case of diabetic cataract is the one reported by Cohen in 1929 in a male infant. The baby developed diarrhea and bloody stools at the age of 5 months. When he was 9 months old glycosuria was discovered and alleviated with 15 units of insulin per day. One month later both lenses were noted to be opaque, and no fundus reflex could be seen.

Another case of diabetic cataract in an 11-month-old infant presenting with nystagmus was observed by Major and Curran in 1925. The diabetic condition was diagnosed when the child was 10 months old. After bilateral discission the nystagmus disappeared. Both fundi were found to be normal and the authors felt they were observing true diabetic lens changes and not congenital cataract.

Though the typical diabetic cataract usually appears in patients under the age of 35 years, cases have been noted in patients as old as 42, 47, 48, 50 and 52 years old (Elschnig, 1924; Franceschetti, 1941; France, 1859; Bücklers, 1939; Schlosshardt, 1950).

The rapidity of cataract formation has been recorded on several occasions. Dor (1877), Litten (1893), and Vinsonneau (1904) saw opacities appear within a few hours. In Jorgenson's case (1947) a sudden loss of vision over a 3-day period brought an 18-year-old boy to his consultation. The patient was unaware of his diabetic condition. The examination revealed a bilateral, advanced subcapsular cataract and the fundus could not be visualized. A blood sugar level of 260 mg. per 100 ml. and a glycosuria of 4 plus was found.

Another dramatic case was reported by Scheffels (1898) of a 15-year-old girl who complained of diminished vision in her right eye of 5 days duration. This symptom was the result of a mature cataract. The lens appeared bluish, silky and swollen with accentuated suture lines. The left lens was absolutely clear. Marked glycosuria confirmed the diagnosis of diabetes. A week later the same girl had to be led by the hand as she had now been totally blind for 4 days. During hospitalization for surgery, operation was postponed as the patient complained of headache. She died within a few hours in coma. Kirby (1933) saw a cataract

develop to the immature stage in 4 days in a 16 - year - old patient, whereas Landabure and Lagleyze (1929) observed a similar phenomenon in 8 days in a 15-year-old girl and a 34-year-old woman, diabetic for 7 and 8 months respectively. In the case of Neuburger (1893) the cataract was complete in 11 days. De Lapersonne (1914) observed maturation of a bilateral cataract within 2 weeks in a 37-year-old woman, a known diabetic for 1 year. Sudden onset of cataract has also been reported by Sedan (1923) in a 50-year-old man. A test for glycosuria performed at once proved to be positive. In this patient the cataract formation was the first symptom of diabetes. The right lens was completely opaque within 1 month and the left one showed several opacities.

Dollfus (1954), and Dollfus and Haye (1957) saw a cataract develop in a young woman within 2 weeks after the discovery of the diabetic condition. Unaware that she was diabetic she had been celebrating Christmas disregarding any dietary consideration. This apparently brought about the coma and the diagnosis of diabetes. By the beginning of January she had bilateral cataract.

Begbie (1861) observed bilateral cataract in a 32- and a 37-year-old woman 3 and 8 months after the first diabetic symptoms of thirst and polyuria were noticed.

Cases of spontaneous disappearance of diabetic cataract are not rare.

In 1870 Seegen observed such a case in a 39-year-old man presenting hazy lenses, 6 months after the diagnosis of diabetes was made. Under treatment in a spa the lenses became clear, but 9 months later the opacities recurred and 3 months later the patient died. In another of his patients, a 55-year-old diabetic woman, the opacities diminished while the patient was under treatment.

In 1885 Tannahill, physician of the prison in Wakefield, England, reported the case of a 43-year-old coal miner who stopped working in the coalpit because of decreasing visual acuity. He was sent to jail for assault and on admission complained of blindness. This was attributed to a symmetrical "nuclear" cataract. The man was a known diabetic for 11 months previous to his imprisonment. While under good medical control in jail his vision began to improve, the opaque lenses gradually cleared and on inspection for discharge no trace of cataract was to be found. One brother of the patient had died of diabetes (Nettleship, 1885).

In a 28-year-old diabetic woman under poor control Alt (1906) observed the development of bilateral lenticular opacities in 1 day. They were subcapsular showing a spoke-like orientation and had a bluish appearance. On a strict diet the opacities disappeared within 2 weeks.

Similar observations were made by Fischer (1925), Braun (1935), Bücklers (1939), Lawrence *et al.* (1942), Schlosshardt (1950), Roberts (1950), Miratynska-Rusinowa *et al.* (1954), Osadchiy (1954), and Turtz and Turtz (1958).

In another instance Legroux (1952) noticed the sudden appearance of white masses in the anterior chamber with blurring of vision in a 50-year-old diabetic woman under poor control. After a few days of insulin treatment the anterior chamber cleared except for some scattered fine precipitates on the anterior lens surface and one posterior synechia. The nature of the white masses could not be explained.

In some instances, initiation of insulin administration coincides with the appearance of lenticular changes as described by Castresana (1931) and by Bücklers (1939). The latter related the case of a 50-year-old man with a glycemia of 350 mg. per 100 ml. Soon after insulin had been injected a sudden drop of vision occurred due to a rosacea-like opacity which had formed in both lenses. These changes receded and finally only a few tiny lenticular opacities persisted.

In a 52-year-old patient Schlosshardt (1950) observed opacities appearing 6 days after insulin treatment had been started and saw them disappear after the 9th day. Overdosage of insulin could not be incriminated.

In a 33-year-old coal miner reported by Hermans (1954) the diagnosis of diabetes was made at the end of July. At that time the patient presented with glycosuria and a blood sugar of 570 mg. per 100 ml. On August 3, a thorough ophthalmologic examination was carried out and revealed old patches of chorioretinitis but no diabetic retinopathy. The lens was clear. The same day the patient was started on a daily dose of 40 units of protamine zinc insulin. Two days later on August 5, he complained of diminished vision which he attributed to the insulin. On examination both lenses showed a bilateral rosacea-like opacity lying in the posterior subcapsular area. All the lens architecture was well marked. The lenticular changes progressed to a maximum 5 days later, then regressed slowly, and disappeared entirely within 6 weeks.

In Jackson's case (1955) a 19-year-old boy with deteriorating vision leading to the diagnosis of diabetes, rapid visual loss took place after insulin administration was started. On the 18th day of therapy the patient experienced two hypoglycemic attacks and the vision at once began to improve. One month later the vision was 6/6 in both eyes.

Neuberg *et al.* in 1958 reported the case of a 52-year-old colored man with abrupt onset of markedly diminished vision within 40 hours after the initiation of insulin therapy and four hours after a transient mild hypoglycemia. At this time, the patient developed large, club-shaped, stellate, radiating opacities of both lenses. At time of discharge 7½ weeks later only a few water clefts remained as evidence of the previous cataracts.

It is often stated that in each case in which diabetic cataracts were found the diabetes had been poorly controlled or uncontrolled for several months or years preceding the development of lens opacities (Boyd *et al.*, 1941; O'Brien and Allen, 1942). Adequate control stopped the progress of opacities after a period of 6 months even if it did not reverse the whole process of cataract formation.

Marr (1952) attributed to better than average control the fact that not one in his series of 67 children, diabetics under the age of 13, showed lens changes. On the other hand careful regulation did not seem to influence the progression of the lenticular opacities in the cases reported by Strouse and Gradle (1924) nor in the groups of 290 and 160 juvenile diabetics studied by Waite and Beetham (1935) and Kumm *et al.* (1950).

The earlier remark by Lecorché (1861) that cataract formation was part of the symptomatology of the severer form of diabetes and therefore indicative of poor prognosis still merits consideration. It has been confirmed that the diabetics

who develop cataract have a tendency to maintain higher blood sugar levels and require larger doses of insulin (Gray, 1933; Waite and Beetham, 1935). Greater doses of insulin *per se* cannot be incriminated in the production of lenticular opacities. Furthermore, in the fatal form of infantile diabetes, the syndrome of Mauriac, characterized by hepatomegaly and renal failure, the patients usually die before eye lesions occur. However, Rosselet and Beck (1958*a*, *b*) observed two cases with diabetic cataract and one with retinopathy.

INCIDENCE OF DIABETIC CATARACT

The statistics of various authors on the incidence of cataract in diabetics varies from 0.03 per cent to 64 per cent (Table 1). Obviously all the observers did not use the same criteria. Some list all "lens changes" in diabetics and attribute them to the disease along with what they call true diabetic cataract. In other cases age is not always clearly defined among patients presenting with cataract in diabetes, and often when a number of true diabetic cataracts is mentioned in younger diabetics the number of young diabetics in the group is omitted. The result is that no conclusion can be drawn from this table.

During the past three decades with improved means of investigation, especially the introduction of the slit lamp, the morphology of diabetic cataract has become more familiar and group studies on the subject more accurate. In Table 2 are listed group studies comprising young diabetics all under 30 years of age and the incidence of true diabetic cataract with one exception (79 per cent) ranges from 0.8 to 31 per cent.

As to the incidence of diabetic cataract in the group of cataractous patients (Table 3) the values are variable (0.04 to 23 per cent). Frequently the other types of cataract involved in these studies are not mentioned. There is also great divergence as to the incidence of diabetic cataract among ocular patients in general, but according to Table 4 is below 15.7 per cent.

However, it appears that cataract is not an infrequent ocular complication in young diabetics. The incidence seems to be related to poor control of the diabetic condition and to the duration of the disease, appearing from 2 years after the beginning of the diabetic symptoms (de Lapersonne, 1914; Joslin, 1923; Gray, 1933; Nobécourt and Ducas, 1933; Bangerter 1938; Boyd *et al.*, 1941, 1942; Rosenbusch, 1945; Cordes, 1952; Lister, 1957). It has been shown (Messinger, 1944; Attiah, 1948; Boulin *et al.*, 1950; Schneider, 1953) that the highest incidence of cataract is during the first 5 years of the disease (11 per cent) and then decreasing during the next 5 years to 2 per cent whereas retinopathy occurs only after the diabetes has lasted 5 to 10 years (4 per cent) and its incidence increases to 14 per cent after a duration of from 10 to 15 years.

Janert *et al.* (1958) grouping their diabetic patients according to age, confirmed that the highest incidence of cataract was in the 20- to 30-year age group. The lowest incidence was noted in the 40- to 50-year group, followed by a gradual increase.

Several authors believe that diabetes favors an earlier evolution of senile cataract (Gallus, 1919; Heuven and Hulst, 1932; Kirby, 1933; Kirwan, 1933;

TABLE 1

Cataract in Diabetics

Author	Diabetics	Cataracts	Percentage
	no.	no.	
1846 Bouchardat[a]	41	1	2.4
1852[a]			
1852 Oppolzer[a]	24	2	8.3
1858 Griesinger[a]	225	20	8.8
1860 Fouconneau-Dufresne[a]	162	1	0.6
1870 Seegen[a]	140	6	4.28
1879 Mayer[a]	169	5	2.9
1883 Frerichs[a]	400	19	4.75
1887 Senut[a]	97	1	1.0
1887 Lagrange[a]	52	13	25.0
1895 König[a]	500	10	2.0
1900 Naunyn[a]	108	1	0.9
1907 v. Noorden	477	62	13.0
1919 Gallus	609		32.5
1929 Landabure and Lagleyze	1091	3	0.03
1931 Sherpardson and Crawford	68		54
1932 Heuven and Hulst	130	43	33
1932 Kirby[b]	88		64
1933 Gray	228	30[b]	13
1934 O'Brien, Molsberry and Allen	126		16
1935 Attiah	135	22[c]	16
1935 Waite and Beetham	297	11[d]	4
1937 Braun	600	3	0.5
1944 Messinger	200	88[e]	44
1948 Attiah	202	11	5
1949 Martensson	154	52[f]	33
1950 Heinsius and Arndt	440		3.9
1950 Kumm *et al.*	160	11[g]	6.8
1950 Martensson and Palm	163	63	38.6
1951 Arndt			3.9
1951 Kennedy and Kirchbaum	133		38.3
1952 Givner			14
1952 Marr	67	6	8.9
1952 Schulte	250		20
1953 Aarseth	288	66[h]	22.9
1954 Miratynska-Rusinowa *et al.*	750		12[i]
1954 Dollfus	1303	83	6.4
1957 Lister	100		42[f]
1958 Babel and Rilliet	320	2	0.6
1958 Janert *et al.*	3000		55.2

[a] According to W. F. Schnyder, 1923.
[b] Two true diabetic cataracts in patients below 36 years.
[c] Six true diabetic cataracts.
[d] All true diabetic cataracts.
[e] Two true diabetic cataracts.
[f] Fifteen true diabetic cataracts.
[g] One-fifth had tuberculosis.
[h] Eleven true diabetic cataracts (8 below 50 years of age).
[i] Of the 12 per cent, 1.7 per cent were true diabetic cataracts.
[j] One true diabetic cataract.

TABLE 2

Cataracts in Juvenile Diabetics under Age of 30 Years

Author	Diabetics	Cataracts	Percentage
	no.	no.	
1934 O'Brien *et al.*	126	20	16
1935 Waite and Beetham	297	11	4
1942 Boyd *et al.*	69	6	9
1942 O'Brien and Allen	260	36	13.8
1945 Rosenbusch	43	34	79
1947 Givner and Lodyjensky	128	1	0.8
1948 Attiah	38	11	29
1948 Chute	13	4	31
1950 Boulin *et al.*	162	8	5
1950 Kumm *et al.*	160	11	6.8
1952 Marr	67[a]	0	0
1957 Dollfus and Haye	360	18	5

[a] Under strict control.

TABLE 3

Diabetic Cataract among Cataracts in General

Author	Patients with Cataracts	Diabetic Cataracts	Percentage
	no.	no.	
1877 Dor[a]	639	5	0.78
	4577	48	1.05
1881 Bono[a]	109	25	23.0
1883 Becker[a]	1100	11	1.0
1884 Landesberg[a]	376	5	1.33
1889 Hirschberg[a]	62	8	12.9
1896 Funke[a]	126	5	4.0
1903 Kako[a]	2135	84	3.9
1929 Elschnig	2525		3
1936 Hagen	1036	53	5
1953 Refatullah	7500	3	0.04

[a] According to W. F. Schnyder, 1923.

von Bahr, 1949; Cordes, 1952; Smith, 1957; Tyner, 1957), while others state that in older diabetic patients cataract is not more frequent than in the general population (Andersen, 1924; Cohen, 1929; Waite and Beetham, 1935; Leopold, 1943; Givner, 1947*a*, *b*).

Investigating cataract formation in two age groups from 10 to 45 years old and from 45 to 88 years old, Dollfus (1954) examined over 1300 diabetics, and the same number of non-diabetic patients chosen at random within the same age group at the Piété Hospital in Paris. The first group included 349 diabetics ranging from 10 to 45 years. He diagnosed cataract in 27 of them, that is, 7.8 per cent. In the second group of 954 diabetics from 45 to 88 years of age he found 56 cataracts, that is, 5.9 per cent, and 6 were typical diabetic cataracts. In the con-

TABLE 4

Diabetic Cataract among Ocular Patients

Author	Patients	Diabetic Cataracts	Percentage
	no.	no.	
1883 Becker[a]	60,000	6	0.10
1887 Badal[a]	20,000	13	0.65
1887 Hirschberg[a]	2,200	4	1.8
1891 Hirschberg[a]	7,176	113	15.7
1903 Kako[a]	36,052	84	2.3
1932 Arruga	20,000	101	5

[a] According to W. F. Schnyder, 1923.

trol group from 10 to 45 years there was an incidence of 1.9 per cent of cataract against 14.5 per cent in the age group 45 to 88 years. Dollfus concluded that cataract formation is more frequent in young diabetics than in the older group of diabetics. Anthonisen (1936) on the other hand observed that the frequency of diabetes in cataractous patients was much greater than in the general population. The author suggested a correlation between cataract and diabetes and concluded that in all diabetic patients with cataract, whatever age they may be, there is little doubt that the cataract and diabetes are related. This seems to be confirmed by Hagen (1936) who found 53 cases (5 per cent) of diabetes among 1036 patients with senile cataract and only 12 cases (1 per cent) of diabetes among 1034 patients with senile glaucoma (glaucoma simplex).

As to the relationship of diabetic cataract and retinopathy Hanum (1939) found lenticular pathology to be 2 to 3 times as frequent in diabetics with retinopathy (34 per cent) as in those without this complication (14 per cent) among 360 young diabetics. Dollfus and Haye (1957) observed 18 true diabetic cataracts, 6 of them in association with retinopathies. Of the 288 patients analyzed by Aarseth (1953) 66 or 22.9 per cent had lens opacities and 34 a concurrent retinopathy. Heinsius and Arndt (1950) found this association in 9 patients out of 17 with cataract while Kirby (1933) states the two complications coexist in 53 per cent of the cases. Schnyder (1923) observed hemorrhages in the fundus of 17 patients among 59 with lenticular opacities. However he stresses the fact that in 5 cases the hemorrhages were probably due to renal involvement. Of 320 diabetics, Babel and Rilliet (1958) found 38.1 per cent with retinopathy whereas only two patients (0.6 per cent) presented with cataract and no retinopathy. The authors believe that there is no parallelism between lens and retinal lesions in diabetes, the two affections evolving independently (Table 5).

In conclusion for the benefit of better future epidemiologic studies of cataract in diabetes it is suggested that standard observations be recorded including the following data: (1) The morphology of the lens changes seen under mydriasis with the slit lamp. Ophthalmoscopic findings are inaccurate, incomplete and unsatisfactory for the diagnosis of diabetic cataract; (2) a drawing of the lens changes; (3) the age and sex of the patient; (4) the duration or onset of di-

TABLE 5

Diabetic Cataract in Diabetic Ocular Diseases[a]

Author	Patients with Diabetic Ocular Lesions	Diabetic Cataracts	Percentage
	no.	no.	
1858 von Graefe	7	4	57.1
1878 Theissier	20	3	15.0
1883 Galezowski	144	46	32.0
1886 Hirschberg	17	4	23.5
1887 Senut	35	1	2.85
1887 Badal	52	13	25.0
1887 Hirschberg	26	4	15.4
1895 König	56	10	17.8
1895 Papanikolau	65	34	52.3
1898 Schmidt-Rimpler	150	68	45.3
1901 Nitzsche	42	22	52.3
1901 Schlink	21	13	61.9
1903 Kako	280	84	30.0
1907 v. Noorden	279	62	22.2

[a] According to W. F. Schnyder, 1923.

abetic symptoms; (5) the state of control; (6) the association of other ocular complications.

Sex Ratio

From Table 6 it appears that since the turn of the century diabetic cataracts have been encountered more frequently in women than in men (52.6 to 72.4 per cent against 47.4 to 26.6 per cent). This seems to be in accord with the sex incidence found in the diabetic population in general, 60 per cent women and 40 per cent men (Brakier, 1952). Furthermore Brakier (1952) in a study of 2346 diabetics covering more than 30 years found a predominance of diabetic women in all age groups.

GENETIC ASPECTS OF DIABETIC CATARACT

No one will dispute the existence of the true diabetic cataract (Gallus, 1919) but not everyone will agree that diabetes is more frequent among cataract patients. That diabetes is usually inherited as an autosomal recessive trait generally will not be contested whereas cataracts have an indefinite heredity. The occurrence of cataracts shows certain hereditary tendencies, but our knowledge of the genetics of cataracts is quite sparse.

Diabetes has both a recessive and dominant mode of inheritance, and it is possible that different genes are concerned in the diabetes of early onset and the diabetes of late onset. Whether the ocular complications of diabetes mellitus are genetically determined or are secondary to the somatic changes produced by the metabolic disorder is not known (Sorsby, 1951). Sorsby feels that there is growing evidence that all diabetics of long standing tend to develop retinal complications,

TABLE 6

Sex Ratio of Diabetic Cataract

Author	Diabetic Cataracts	Male	Percentage	Female	Percentage
	no.				
1870 Seegen[a] 1858–59 v. Graefe[a] 1896 Funke[a] 1899 Zeller[a] 1901 Nitzsche[a] 1903 Kako[a]	238	132	55	106	45
1903 Kako[a]	84	57	67.8	27	32.2
1919 Gallus[b]					
1923 Schnyder	59	28	47.4	31	52.6
1929 Elschnig					3M:5F
1932 Heuven & Hulst	43	18	41.8	25	58.2
1949 Martensson	15	4	26.6	11	73.4
1950 Heinsius & Arndt[c]					
1953 Aarseth	11	3	27.2	8	72.8
1953 Schneider	27	3	11	24	89
1957 Dollfus and Haye[d]					
1958 Janert *et al.*[e]					

[a] According to W. F. Schnyder, 1923.
[b] Predominance of female.
[c] Predominance of female between 13 and 35 years of age.
[d] No sex predominance.
[e] Predominance of female.

and while this is suggestive, it is by no means conclusive of the possibility that these changes are genetically determined.

In analyzing 675 family histories, Pincus and White (1933) presented quantitative evidence showing that susceptibility to diabetes is probably determined by a recessive gene. Among 45,650 consecutive selectees and volunteers (18 to 45 years) Blotner *et al.* (1943) found 208 diabetics, and 126 subjects with transient glycosuria. A familial history of diabetes was about six times as frequent in the diabetic patients (32 per cent) as in the nondiabetic patients used as a control (5.2 per cent). In the United States, 5 per cent of the population is homozygous for the gene determining susceptibility to diabetes (Steinberg, 1958). Only 1 per cent is recognized to be diabetic, whereas an additional 1 per cent of the population is diabetic, but not recognized as such (Joslin *et al.*, 1952). Hence some 60 per cent to 90 per cent of those who are genetically liable to diabetes are not recognized by present routine methods of examination. De Lapersonne and Velter (1920) described the formation of cataract in a man with glycosuria. His two children, mother and sister as well as a deceased daughter, were affected with a similar visual affection. The father presented with a bilateral zonular cataract and glycosuria, whereas his 8½-year-old daughter and 5½-year-old son had identical lesions of the lens consisting of bilateral, anterior polar congenital cataracts and glycosuria.

Cataract and diabetes are at times genetically linked. The problem of the heredity of diabetic cataract remains to be elucidated. In order that we might investigate further the genetics of diabetic cataract, we searched the literature for cases of diabetic cataract in univitelline twins. Unfortunately, this investigation remained fruitless, but we came across the publication of Aoyama (1932) who found seven cases of diabetes among 13 children of apparently healthy parents. Five of these children presented with cataracts.

There are many examples in the literature of the hereditary nature of diabetes and Ghalioungui (1948) found a family history in 55 per cent of his cases. Burnstein and Patterson (1949) described 55 diabetics among 161 direct descendants of a couple developing the disease at the ages of 58 and 60. Of their 10 children, 1 died at the age of 20, possibly in coma, and 5 others became diabetic. In the third generation in two sets of identical twins, each member of the pair became diabetic within a few weeks of the other, one at age 6, the other at age 12. The authors suggest the Mendelian dominant mode of heredity. Allan (1955) observed two sets of twins, one pair uniovular, the other pair binovular, all suffering from diabetes mellitus. Diabetic twins are uncommon and 80 per cent involved are of the uniovular type. Almost without exception, in uniovular twins both members are said to suffer from diabetes after the age of 43, if one of the twins develops the disease. Allan concludes that this study favors the recessive mode of transmission following the Mendelian law.

Various authors in their observations of the pathogenesis of senile cataract have mentioned deranged carbohydrate metabolism as an important factor, basing their opinions on the frequent finding of abnormal glucose tolerance curves in cataractous patients (Langdon, 1922, 1925; Baldwin and Barthel, 1924; O'Brien, 1928, 1931, 1932; Malkin and Krassikov, 1927; Galindez, 1929; Palmerini, 1931; Bellows, 1944). Many others have not been able to confirm this point of view (Lottrup-Andersen, 1929; Waite and Beetham, 1935). In reality, many of the studies advocating this possibility have been incomplete, but some of the statistics are beyond reproach. That the so-called prediabetic state gives rise to ocular pathology can no longer be disputed.

Conn (1958) in a recent article found that among 387 apparently healthy relatives of known diabetics, 18 per cent are diabetic without knowing it and another 4 per cent are probably diabetic. Of 125 subjects with no known family history of diabetes, only 1 subject showed a diabetic glucose tolerance test and only one more had a curve indicating that he was probably diabetic. The above patients were all aglycosuric and had normal blood sugars, but presented pathologic glucose tolerance curves. In addition, among 259 relatives of diabetics who showed a normal glucose tolerance curve, a cortisone glucose tolerance test (CGT) was done and 25 per cent gave a positive response as compared to a 3 per cent positive response in a control group. Conn concludes that without question there is a hereditary aspect involved in diabetes mellitus and that the prediabetic state exists from the moment that the ovum is fertilized to the time we can justify a clinical diagnosis by whatever means. Hoet (1954) and others have emphasized the importance of the environment *in utero* upon the fetus. It has been suggested

that this congenital aspect, that is, the as yet unknown abnormality contained in the prediabetic mother which influences the fetus, may have even greater importance than the hereditary one itself.

We can no longer have any doubts as to the existence of a prediabetic state. However, Conn points out that an abnormal CGT test does not make an individual a prediabetic, even though a certain number may develop the clinical disease.

Paufique and Guinet (1957) reviewed a series of their own cases of retinovitreal hemorrhages and cataracts in young patients considered as prediabetics. None of these patients was ever found to be glycosuric or have an elevated blood sugar. However, all of them had pathologic glucose tolerance curves and most of them a family history of diabetes. One of the patients aged 51, could be classified as presenting a senile cataract. The only anomaly found was an abnormal glucose tolerance curve and a diabetic father. The four other cases aged 44, 41, 35 and 27, all presented with typical endocrine type cataracts and all had abnormal glucose tolerance curves. The opacities began as subcapsular, punctiform, flaky opacities. The authors conclude that in every young subject with lens opacities or retino-vitreal hemorrhages and no apparent explanation, a glucose tolerance curve should be performed.

Thus, it can be affirmed that definite changes in the lens and retina do take place in conjunction with the prediabetic state. This mild derangement of carbohydrate metabolism, which may eventually evolve into the classical picture of diabetes mellitus, is apparently of a sufficient order to cause changes in the lens and retina. The various mechanisms which have been invoked to help explain cataract formation as well as development of retinopathy in diabetes such as hyperglycemia, acidosis, and osmotic factors do not seem to apply. The intrinsic derangement would in this particular instance seem to involve the whole organism on a cellular level, perhaps tracing its origin back to the fetus.

EXPERIMENTAL DIABETIC CATARACT

Weir Mitchell in 1860 noted "the formation of a peculiar variety of cataract as one of the most curious and striking symptoms attendant upon the sugar poisoning when sugar, in one way or another, was introduced in considerable amount into the system of the frog."

Wessely (1919, 1922) observed the first really pure diabetic cataract in a depancreatized dog maintained for a year after the procedure. Chaikoff and Lachman (1933) observed a diabetic cataract in 8 out of 10 dogs after pancreatectomy and maintained with insulin. The authors believed that the lens changes appeared a year or two after onset of the disease. Foglia and Cramer (1944) related the lesions in the lens to the severity of the diabetes. The amount of research done on cataract in diabetes is enormous, and we will attempt to review rapidly the highlights as well as to correlate the findings in so far as they are applicable towards an understanding of the pathogenesis of the lens changes in the human disease.

Sheehan in 1932 studying the effect of a synthetic styrilquinoline on rabbits in

reference to its antitrypanosomal effect, noticed that it produced a nephritis as well as necrosis of the β-cells in the islets of Langerhans. However, the substance was regarded as an accidental finding. Eleven years later, Dunn, McLetchie and Sheehan described a method of producing an experimental diabetes by specific necrosis of the β-cells in the islets of Langerhans. This experimental procedure has remained extremely popular and numerous observations are available as to the various aspects of alloxan diabetes. It was not very long before the ocular complications of alloxan diabetes were reported in the literature. Bailey, Bailey and Hagan (1944) described the lesions in the islets of Langerhans of the rabbit induced by alloxan, at frequent intervals following its administration. This study indicated that the pancreatic lesions begin almost immediately after injection and that they are degenerative from the start. These changes are already apparent in the initial hyperglycemic stage and in the hypoglycemic stage they progress to a point where they approach those of the diabetic phase. In the same year, Bailey, Bailey and Leech reported the appearance of cataracts in four to six weeks in five rabbits previously injected with 200 mg. per kg. I. V. of alloxan. These authors found the minimal diabetogenic dose of alloxan in rabbits to be 40 mg. per kg. injected on repeated occasions. Schneider *et al.* (1945) observed lens changes in 15 alloxan-diabetic rabbits. The alterations were at first in the form of peripheral vacuoles, becoming more numerous and encroaching upon the central area of the lens, progressing in direct proportion to the duration of the diabetes. The authors found that the lens manifestations continued in spite of insulin and vitamin therapy, though at a slower rate. However, Kok van Alphen and Cohen (1950) determined that if the diabetes in the rat was controlled with insulin, cataract failed to develop. Cramer and Foglia (1948) in a series of pancreatectomized rats, showed that the rate of development of cataract in these rats was dependent upon the amount of pancreas removed and the intensity of the diabetes. In no case did retrograde changes take place after the cataract was formed. Supplementing the diet of alloxan diabetic mice with 40 per cent galactose or dextrose increased the occurrence of diabetic cataracts. In these mice Yaso (1951) noted extreme degenerative changes in the pigment epithelium layer of the ciliary body and iris, as well as degenerative changes in the lenticular epithelium and fibers.

Babel (1951, 1953) gave a detailed description of the clinical aspects of the alloxanic cataract in mice and rabbits, emphasizing the importance of the vacuoles and the signs of endocrine cataract in the posterior cortex.

Bellows and Shoch, (1950) Kok van Alphen and Cohen (1950), Janes *et al.* (1952), Babel (1951, 1953) and Bounds *et al.* (1955) have also given biomicroscopic descriptions.

The lens changes observed by Babel developed very slowly in some of the animals; the first lesion appeared about the 14th week after alloxan injection. In other rabbits a marked aqueous flare could be seen on the 3rd day, disappearing in 8 to 10 days. The lens at that time was absolutely unaltered, and in one of these rabbits the first subcapsular vacuoles appeared on the 18th day. Babel is of the opinion that the lens changes are not the result of the alloxan for the fol-

lowing reasons: (1) the injected alloxan disappears rapidly from the blood and the aqueous humor, (2) cataract results only if the animal becomes diabetic, and (3) glutathione and cysteine participate in the pathogenesis of this form of cataract. Babel (1955) drew attention to the ocular repercussions of the metabolic disturbances in fat and protein metabolism. The marked aqueous flare during the first few days following upon the administration of alloxan, is due partially to neutral fat in the anterior chamber. Chromatographic studies of the aqueous revealed altered patterns in two of the amino acids, with an important accentuation of the valine and leucine spots. The distribution of the other amino acids was apparently normal. This augmentation of the amino acids was only temporary, and reached normal levels in a short time.

Naidoff *et al.* (1955) noted lens changes within 48 hours after the injection of alloxan, if dilatation of the pupil was sufficient. The lens changes were correlated with fluctuations in the urinary and blood glucose levels, and could be controlled by insulin therapy. The authors' studies on DDD (2,2-biparachlorophenyl)-1,1-(dichloroethane) which also tends to lower blood sugar levels in alloxan diabetic rats suggest that a coincident regression in cataracts occurs.

Von Sallmann (1957) remarked that in galactose and alloxan cataract, as well as in cataracts caused by tryptophan deficiency, the lens epithelium in the germinative zone is but little involved with the exception of its mitotic activity. This effect on cell division does not seem to contribute to the extensive lens fiber changes. New normal lens fibers are formed upon withdrawal of the injurious factors and residues of the damage are confined to circumscribed layers of the lens cortex. Von Sallmann *et al.* (1958) described the morphology of the alloxan-induced cataract. The aim of the authors was to determine the role the epithelium of the lens plays in the pathogenesis of experimental and senile cataract, that is, studying and relating epithelial and bow pathology with the fiber changes and identifying the anatomical substrate of the clinically observed opacities.

The changes in rat lenses seven days after the injection of alloxan in rats with a blood sugar level of 794 mg. per 100 cc., consisted of hydropic fibers under the anterior lens capsule as well as fiber destruction with vacuole formation in the middle layers of the bow area. At an early period and in the following weeks, the cystic spaces were confined to a layer midway between the nucleus and capsule of the lens. Subsequently excessive swelling of cell components in the anterior cortex took place and only in the most advanced stages did analogous changes take place in the posterior cortex. The sections showed multilayered arrays of the epithelium, mostly at and around the anterior pole, but at times involving other sites on the anterior surface. The lenses were examined at 7, 14, 21, 28 and 35 days after the injection of alloxan.

Von Sallmann *et al.* do not agree entirely with Babel on the vulnerability of the subcapsular young fibers at the lens equator. The authors point out that the most superficial fibers seem not to be damaged by the toxic agent as the area of hydropic swelling and disintegration of the fibers is regularly noted in the deeper part of the cortex at the bow area and is separated from the surface by a layer of

normal fibers and nuclei. However, in one of the histologic slides presented by the authors, hydropic fibers are seen directly beneath the lens epithelium, and even though the vacuoles are seen extending deeper in the lens cortex, the young, dividing, subcapsular fibers seem definitely involved.

Ogino *et al.* (1957) studied the clinical and histologic changes in cataracts induced by the different quinoid substances, quinonimine-carboxylic acid, benzoquinone-acetic and 2-amino-*p*-quinonimine. The changes observed were similar to other cataracts induced by various agents, as galactose, naphthalene, alloxan or dinitrophenol. In all these experimental cataracts, hydropic lens fibers are found as the earliest recognizable alteration in the lens cortex. Rupture and dissolution of the hydropic cells can be seen in the more advanced stages, leaving interfibrillar clefts with protein coagulum. The chronologic studies described by the authors indicate that the so-called "balloon cells" migrate from their site of origin at the equator to the anterior and posterior poles. Swelling and degenerative changes in the equatorial subcapsular cells, as well as abnormalities of the subcapsular epithelium were observed. The authors believe as a result of their experimental work that the onset of senile cataract is closely related to abnormal metabolism of tryptophan and one of these metabolites could be demonstrated in patients with senile cataract. The abnormal metabolism of tryptophan may however result from a primary abnormality in carbohydrate metabolism.

Glutathione is found in the normal lens at a very high concentration, but its function in cellular metabolism is still a matter of speculation, though it seems to play an important role in maintaining the functional thiol groups of certain enzymes in their reduced state. It is known however that the concentration of glutathione in the lens diminishes progressively in the formation of cataract. When alloxan is injected into the blood stream it disappears rapidly within 2 to 3 minutes. Simultaneous to the disappearance of reduced glutathione from the red blood cells (Leech and Bailey, 1945), Bellows and Shoch (1950) found that glutathione in the lens unlike that in the blood is not appreciably affected after alloxan injection. In the rabbit the first sign of a decrease in the lens reduced glutathione (GSH) occurs three days after administration of alloxan. If diabetes does not develop as a result of alloxan injection, then the decrease in lens GSH does not take place. Kinsey and Merriam (1950) explained the decrease in concentration of glutathione in the lens following naphthalene feeding on the basis of an inhibition of resynthesis.

Waters (1950) injected alloxan into rabbits but observed that there was no significant decrease in the glutathione content of the lens, despite the fact that half the animals developed bilateral cataract. These results are diametrically opposed to those of Bellows and Shoch (1950). The protein sulfhydryl content of the lens decreased immediately after injection of alloxan and did not become normal for as long as two hours. Waters suggests that alloxan combines with SH groups.

Mitchell and Dodge (1935) fed rats on a diet consisting of 70 per cent lactose as the sole carbohydrate. Bilateral cataract occurred in 68 per cent of the rats. No cataract was produced after feeding with starch, maltose, dextrin or saccharose

in the same concentration. The total serum calcium was not changed. Mitchell (1935) explained that galactose injured the lens epithelium, increasing the permeability to various inorganic ions. Yudkin and Arnold (1935*a* and *b*) made the same observations. They remarked that in young rats the opacity was nuclear, whereas in older rats the opacity was in the cortex.

Bellows (1936) found that galactose in some way causes a loss of the sulfhydryl content of the crystalline lens. As a result of this, the internal oxidative system of the lens reaches a stage where it is insufficient to support the life of the tissues. Death of the lens fibers occurs with resulting opacification. Cysteine and to a lesser extent vitamin C delay the onset of galactose cataract. The sulfhydryls (glutathione and cysteine) are diminished quantitatively in the lenses of rats fed galactose, even before there is any visible change. Bellows and Rosner (1936) isolated glutathione from the lens in pure form for the first time. Young rats were found to be more susceptible to galactose cataracts. Their strain was also important, and in general a high protein diet retarded the onset of galactose cataract, a low protein diet hastening the onset. Mitchell and Cook (1937 and 1938), Gifford and Bellows (1939), Yudkin and Greer (1940), Riggs (1954), Tojo (1954) all noted that the earliest changes in galactose cataract involved the cortical fibers near the equator, but the growth of new fibers was rapid enough so that some relatively normal fibers were always found just beneath the capsule in this region.

The capsular epithelium showed changes later, whereas the nucleus was unaltered until an advanced stage in the process. Regeneration of new fibers occurred rapidly when a normal diet was resumed. Galactose does not produce cataract in rats if given subcutaneously (Selle, 1940), but Bakker (1939) noted that if galactose was added to the medium of a lens culture *in vitro*, fine opacities appeared underneath the capsule within four days. In a control culture *in vitro* with only glucose in the medium, no opacities were visible even after nine days. Following the ingestion of galactose in rats, this sugar can be found 24 hours later in the lens and aqueous humor, whereas the glucose content of the lens is lowered (Ching, 1941). Craig and Maddock (1953) used a very highly concentrated (70 per cent) galactose diet, producing peripheral lens opacities in 9 days and central opacities in 20 days, as well as corneal vascularization, iritis, testicular atrophy and hydronephrosis.

Rats fed on a diet containing 50 per cent galactose, consistently produced cortical cataracts and injections of fresh proteins failed to modify their evolution (Rouher and Tronche, 1954). Sterling and Day (1951) noted that xylose was more effective than galactose as a cataractogenic agent, whereas cataract development was slower in diabetic rats even though the blood sugar was higher.

Tyrosine given to scorbutic animals does not produce cataract. If 2 per cent galactose or xylose is added to this regimen, cataract does develop accompanied by the excretion of homogentisic acid and benzoquinone acetic acid in the urine. Glucose does not have this effect in scorbutic animals, nor does 2 per cent galactose or xylose fed alone (Tojo, 1955).

Pregnant female rats were fed a diet containing 25 per cent galactose. Lens

changes appeared in the embryo and the primary area of degeneration was localized in the lens nucleus, which according to many authors is characteristic of cataract in the young (Bannon *et al.*, 1945).

Yudkin and Arnold (1935*a*) found that in young rats the initial opacities occurred in the nucleus, whereas in older rats a cortical cataract appeared. Apparently, the sequence of cataractous changes in the embryo is clearly related to developmental changes within the lens.

Quednau (1956) remarked that experimental cataracts, and particularly those due to a high dietary content of galactose or xylose, can be induced only in young animals and almost exclusively in rats. Embryonal conditions exist in these animals up to the 28th day, as the posterior surface of their lens is still supplied by a fine network of blood vessels branching off the anterior hyaloidea. However, many authors contest the concept that these embryonal conditions are responsible for the nutritional cataracts, basing their opinion on reports that galactose cataract can be produced in older rats and even rabbits.

Diabetes can also be induced in the experimental animal by the injection of dithizone, producing cataracts similar to that in alloxan diabetes (Gambassi *et al.*, 1952; Dell'Acqua and Gambassi, 1952*a*, *b*; Butturini *et al.*, 1953; Sbordone, 1958). Cysteine injected five minutes before dithizone protected the rabbits from diabetes (Baumgarten *et al.*, 1952).

The hexokinase activity of the lens is diminished during the diabetes provoked by dithizone and becomes especially marked with the appearance of the opacities (Mandel and Quaranta, 1958).

Patterson (1951) injected dehydroascorbic (DHA), dehydroisoascorbic or dehydroglucoascorbic acid producing hyperglycemia in rats. Preinjection of sulfhydryl compounds did not offer any protection. The lenticular opacities appearing in alloxan and DHA diabetes in rats seem to be very similar to those in rats after pancreatectomy as well as in the human diabetic cataract (Patterson, 1952).

The disturbance of normal carbohydrate metabolism by grossly different experimental methods results in cataracts of a similar morphologic picture. Gifford and Bellows (1939) and Friedenwald and Rytel (1955) comparing the histologic alterations of alloxan diabetic, galactose, and radiation cataracts, found hydropic cells in a zone somewhat beneath the surface in the equatorial region of the lens. However, this zone was narrower and more deeply located in the galactose and diabetic cataract. Hydrops of the lens fibers represents the earliest change in the lens cortex in the development of these cataracts.

Interference with sugar metabolism is always followed by some cataractous changes, and this can be demonstrated by the use of such various substances as monoidoacetic acid, sodium fluoride, sodium malonate, phloridzin or fluoroacetic acid. The inhibition of carbohydrate metabolism is effected in a different way by by each of these compounds. Yet opacities result in all cases, demonstrating that the lenticular changes are not the result of a toxic phenomenon, but of interference with carbohydrate metabolism (Nordmann, Mandel and Achard, 1954).

The biochemical changes in the lens as a result of human or experimental

diabetes are many, and valid comparisons in both types can be made. We will examine the methods available to prevent or alter the evolution of the experimental diabetic cataract so that we may better understand its pathogenesis. As already mentioned, deviations of carbohydrate metabolism result in opacities of the lens, and the trend of thought at present is towards a common mechanism of cataract formation initiated by various causes.

The relationship of alloxan diabetes to the human disease has given rise to much speculation. Alloxan is absorbed from the alimentary canal in rats and the changes in the islets of the pancreas are the same as when alloxan is administered systemically (Ruben and Yardumian, 1945). Alloxan is found in its half reduced form, alloxantin, in crude beet juice (Ruben and Tipson, 1945).

In 1932, Fisher and Johnson demonstrated the presence of convicine in broad beans (vicia faba), which on acid hydrolysis yields alloxantin. Thus, a substance capable of giving alloxantin was found in nature. Alloxan is readily prepared *in vitro* by the action of certain oxidizing agents on uric acid (Ruben and Tipson, 1945). Alloxan was also shown to be present in normal animal livers (beef, calf, domestic fowl, guinea pig, lamb, rabbit and rat). Diabetes resulted in rabbits injected with dialuric acid (Bailey, Bailey and Leech, 1946), as well as with methyl alloxan, alloxantin, dimethylalloxantin or methyl dialuric acid (Bruckmann and Wertheimer, 1945 and 1947). The case for human diabetes being possibly of alloxan origin seemed attractive especially since uric acid is part of normal human metabolism. However, Brunschwig *et al.* (1943, 1944) could not produce any conclusive evidence that the β-cells in the islets of Langerhans in man could be permanently destroyed by the intravenous injection of even large doses of alloxan. In one patient, an attempt was made to destroy an islet cell carcinoma but this was ineffective and the hypoglycemic crises persisted.

Certain substances when injected immediately preceding alloxan will impede its diabetogenic action. BAL or 2,3 dithiolpropanol (Tislow and Chesler, 1947), 3,4-diaminotoluene, orthophenyldiamine and sodium bisulfite (Weinglass *et al.*, 1945), methylene blue (Highet and West, 1949), and adrenaline (Maske *et al.*, 1953) will prevent the apparition in most animals of alloxan diabetes. BAL per os or subcutaneously will also exert a protective action (Chesler and Tislow, 1947). Lazarow (1946) reported that the intravenous injection of large doses of glutathione (2500 mg. per kg.) or cysteine (912 mg. per kg.) 1 to 2 minutes before injection of a diabetogenic dose of alloxan, completely protected rats from diabetes (Patterson *et al.*, 1949). Other amino acids, phosphate buffer and ascorbic acid did not exert such a protective effect.

When the sulfhydryl compounds were given 1 minute after the alloxan injection, partial protection occurred, whereas after 3 minutes or more, no protection resulted. The islets of diabetic rats 5 to 7 minutes after injection of alloxan when examined histologically with the usual stains, appeared essentially normal. However, with special granule stains, a marked decrease in β-cells became evident (Duff, 1945). De Caro and Rovida (1937) reported that within 10 minutes following injection of 200 mg. of alloxan into rats, the glutathione content of the

liver fell to 17 per cent and that of the intestine to 42 per cent of the normal value. After intravenous injection of 200 mg. per kg. of alloxan in rabbits, blood glutathione decreases rapidly, in some cases to zero. An immediate reaction takes place between alloxan and blood reduced glutathione, with the tendency for complete disappearance of both (Leech and Bailey, 1945). Within 5 minutes after the injection, the blood glutathione values began to rise and returned to normal in 18 to 24 hours. Lazarow (1946) concludes that the action of glutathione and cysteine may consist in protecting the sulfhydryl groups of the islets cells from inactivation by alloxan. However, ascorbic acid does not protect against alloxan, even though it reduces alloxan to dialuric acid *in vitro* (Ruben and Tipson, 1945). Friart (1955) believes that the direct action of the SH group is not involved, but that a linkage of the S—S radical and alloxan takes place.

Apparently the entire nicotinic acid molecule can inhibit the diabetogenic action of alloxan by combining with it (Banerjee, 1947). Vitamin E was found to have an effect on the development of alloxan diabetes and cataract (Alagna, 1952). A group of rabbits started on vitamin E before alloxan had less severe diabetes and only one in six developed cataract. Other rabbits treated with vitamin E after diabetes was established also had less severe diabetes and three in eight showed cataracts. Desoxycorticosterone acetate impeded the development of cataracts in alloxan diabetes, and nicotinic acid, riboflavin, vitamin E and corticotropin moderated the onset and evolution of cataracts in dithizone diabetes (Alagna, 1954*a*, *b*). Alloxan washings inhibit glucose uptake, glycogen synthesis and oxygen uptake by diaphragm isolated from vitamin E deficient rats. This inhibition can be partially overcome (glycogen formation) or almost completely (glucose uptake, oxygen uptake) by the presence of sufficient vitamin E in the diet of the animals. Gray and DeLuca (1955) suggest an antagonistic action of alloxan and vitamin E. As soon as definite cataract formation was observed in adult rats, 7 to 14 weeks after the subcutaneous injection of a diabetogenic dose of alloxan, insulin treatment of the animals was installed (2 to 8 units per day of ordinary and protamine zinc insulin). Marked regression of the cataracts took place with insulin therapy in seven out of eight animals (Cohen and Kok van Alphen, 1953). Rats with chemically induced diabetes ordinarily develop cataract within 2 to 3 months. Patterson (1955) placed such rats on a diet of 50 per cent fructose, 25 per cent corn oil and 25 per cent casein fortified with vitamins and minerals. Cataracts were prevented and growth rate accelerated, and the author concludes that the basic deficit results from inadequate glucose utilization in the absence of insulin. The rate of injection of alloxan is important if diabetes is to follow. Too slow an injection rate has no effect whereas a rapid injection kills many of the animals (Pincus *et al.*, 1954).

Alloxan at a concentration of 0.2 per cent is most active in stimulating the oxygen consumption of erythrocytes, but inhibits by more than 50 per cent the action of cytochrome oxidase. The addition of cytochrome *c* in the presence of alloxan does not increase the oxygen consumption; thus one may assume that alloxan specifically blocks the cytochrome-cytochrome oxidase system and does not act by influencing other enzyme systems which may be present (Robuschi, 1952).

Karaki (1954) described the atrophy of the Golgi apparatus in the ciliary epithelium of alloxan diabetic rabbits with cataracts. The same author reported in 1956 on changes in the lens and other ocular tissues of alloxan diabetic rabbits with special reference to the changes in the Golgi apparatus and mitochondria. Degeneration of lens epithelium with subepithelial vacuolization at the equator takes place in the early stage of alloxan diabetes, followed by a hypertrophic regeneration of the epithelium causing cataract development. Karaki observed that during the stage of degeneration the Golgi apparatus disappeared accompanied by deformation and reduction of the mitochondria in the epithelial cells. The changes in the iris and ciliary body were slight and appeared only in the later stages of cataract development.

Nordmann, Mandel and Schmitt (1955) rendered 4-month-old white rats diabetic with alloxan. Insulin was given regularly except during the last 2 days before examination. The lenses were checked at 8 and 21 days after the alloxan injection. After 1 week the lenses were still clear whereas after 3 weeks, fine punctate opacities appeared. The authors believed that the lenticular changes were probably the result of the lack of available energy due to modification in enzymatic activity of the carbohydrate cycle, namely restriction in hexokinase activity (71 per cent) and increased activity of adenosine triphosphatase (83 per cent). The failure of hexokinase impairs the initial phosphorylation of glucose, whereas hyperactivity of ATPase favors decomposition of ATP, causing an imbalance and reduction of available energy followed by faulty distribution in amino acid arrangement.

Crude extracts of the anterior pituitary contain a hexokinase-inhibiting factor, which can block the formation of glucose 6-phosphate, essential for further metabolic steps (Colowick *et al.*, 1947). Insulin has no direct action on hexokinase but is an inhibitor of the hexokinase-inhibiting factor. Thus, the inhibition of hexokinase activity is reversible by means of insulin. This was the first evidence of a biochemical site of insulin action, and introduced the important concept that hormones regulate through their effect on enzymes.

The uptake of glucose by lenses obtained from diabetic animals is reduced to 45 per cent of the normal level (Macintyre *et al.*, 1956). This significant decrease is observed within 7 days after the induction of diabetes and represents one of the early metabolic changes in the lens. Addition of insulin to the incubating medium has no effect on the uptake of glucose by the lens, but it has been suggested by the authors that insulin may act through some other substance. Ross (1953) has observed an insulin effect on decapsulated rabbit lens.

Drabkin (1948) summarized the role of phosphatases in diabetes. The increased activity of the liver phosphatases in alloxan-diabetic rats and their restoration to normal by effective insulin therapy suggested to Drabkin and Marsh (1947) that the phosphatases have a significant role in the diabetic state. A relationship has also been demonstrated to exist between the level of blood sugar and the phosphatase activity in the kidney (Marsh and Drabkin, 1947) and blood serum (Cantor *et al.*, 1947). Drabkin proposed the hypothesis that the renal threshold for glucose was at least in part an expression of the limit to which phosphatase activity can be raised. Beyond this limit tubular reabsorption

is incomplete and spilling of sugar into urine takes place. Thus the renal threshold for glucose becomes a dynamic function under enzymatic control. Phosphatase activity is excessive in alloxan-diabetes and glycogenolysis is favored.

Allen and Friedenwald (1953) demonstrated the presence of substrate-specific alkaline phosphatases in the ocular tissue, including lens of rabbits.

There is some evidence of a decrease in the ATP content of the tissues of diabetic rats (Charalampous and Hegsted, 1949). A diminished ATP content, that is, decrease of high energy phosphate is noted in rat lenses made cataractous with either alloxan or galactose. In two species (rat and rabbit) and in two differently induced experimental diabetes (dithizone and alloxan) Mandel *et al.*, (1956) observed an increased consumption of pyruvic acid and an increased ATPase activity. The authors explain that the increased utilization of pyruvic acid is probably the result of an enzymatic adaptation resulting from the metabolic disturbance caused by the diabetes. The increased ATPase activity is conditioned by the integrity of the lens fibers and disappears at the slightest evidence of lens opacification.

Nakamura (1956) confirmed previous findings that the lens cortex shows a more active metabolism of pyruvate than the nucleus and capsules. The process of pyruvate oxidation is most active in the epithelium and cortex of the lens. According to the author, the cortex followed by nucleus and capsule have the most pronounced enzymatic activity within the lens.

During the diabetic state induced by dithizone in the rabbit, there is a significant lowering in the concentration of ribonucleic acid and desoxyribonucleic acid in the lens, which may play an important part in the pathogenesis of the dithizone-diabetic cataract in view of the close relationship existing between the dynamic state of the proteins and these acids (Mandel and Quaranta, 1957).

Cataract in human galactosemia has been frequently investigated. Hartstein (1958) reported that feeding galactose in human beings during periods varying from 2 to 12 months did not cause cataract. Galactose 1-phosphate (galactose-1-P) accumulates in the red blood cells of galactosemic infants on a milk diet. At the same time the oxygen uptake of these cells is partially inhibited. Schwarz and Goldberg (1955) suggested the possibility of galactose-1-P acting as an inhibitor of glucose metabolism, but the correlation of diminished oxygen uptake and galactose cannot be determined as yet.

In their experiments, the authors found that control lenses or capsules contain a maximum of 0.08 μg. galactose-1-P per capsule. Young male albino rats were fed a diet containing 30 per cent galactose and were killed at various intervals. Whole cataractous lenses contained approximately the same amount of galactose-1-P as did separated capsules, that is, 1 μg. per capsule. The galactose-1-P seemed to be confined to the lens epithelium and capsule. Schwarz and Goldberg found that in noncataractous lenses from galactose-fed animals the amount of galactose-1-P found was similar to that of normal animals.

In a review of the literature, Johnson (1953) noted that 12 out of the 13 reported cases of galactosemia since 1945 showed lens changes. The sole exception was treated at the age of 2 weeks. The author was unable to correlate patient

age and type of lens change, but noted that the withdrawal of milk before the age of 8 months was necessary to prevent irreversible opacities.

Schwarz *et al.* (1955) suggested that the metabolic block in galactosemia was due to failure to convert galactose-1-P into glucose-1-P.

The morphology of the lens changes in human galactosemia can vary from a ring-like lamellar opacity with or without vacuoles in the anterior cortex to zonular and nuclear opacities (Falls *et al.* 1951; Patz, 1953). In galactosemia, there is a relative or absolute lack of the enzyme galactose-1-P-uridyl transferase, transforming galactose-1-P into glucose-1-P. This results in marked accumulation of galactose-1-P in the liver and red blood cells. Lerman (1959) examined a 4-year-old boy showing the typical picture of congenital galactosemia, with lens changes consisting of a slight degree of opacification localized to the anterior cortical region and extending towards the equator. The child died and the lenses removed within 1 hour after death were assayed for galactose-1-P-uridyl transferase and uridine diphosphate galactose (UDP-galactose) pyrophosphorylase. A complete lack of galactose-1-P-uridyl transferase activity was found in the galactosemic lenses, whereas the level of UDP-galactose pyrophosphorylase is apparently elevated.

Lerman emphasized that in the normal person, it seems unlikely that galactose would be an important constituent in lens metabolism, since the ingested galactose is quickly converted to glucose by the liver before it could rise to any significant level in the lens. In the milk fed infant the lens is probably called upon to handle galactose to a much greater extent than in later life. The absence of galactose-1-P-uridyl transferase in such a lens can therefore result in a very rapid accumulation of galactose-1-P. Lerman demonstrated a marked diminution in the succinic dehydrogenase activity in the epithelium of the lens of his patient with galactosemia, substantiating the belief that the oxidative metabolic cycle is seriously embarrassed in the galactosemic lens by the accumulation of galactose-1-P. Dische *et al.* (1956, 1957) in their studies on experimental galactosemic cataract have shown that the synthesis of soluble protein is depressed from 60 to 100 per cent and that this inhibition coincides closely with the beginning of galactose feeding. The mother and only brother (age 7) of the patient showed a marked depression of erythrocyte transferase activity. Minimal lenticular opacities situated in the deeper layers of the anterior cortex were seen in the lens of the mother, who was aware of these changes since childhood. Galactose tolerance curve of mother and brother were normal.

(In the next issue of the SURVEY, the authors will discuss the pathogenesis of diabetic cataract in man and will also present a comprehensive bibliography.)

Clinical Practice

VITREOUS

SOME INVESTIGATIONS ON THE CELLS OF THE VITREOUS BODY

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The problems and controversies surrounding the cells of the vitreous body are probably due to the influence of two factors in the work of the investigators. These are (1) the special technical aspects of the mode of investigation, and (2) the fact that the findings cannot be compared with analogous conditions elsewhere in the body. In regard to the first of these, it may be said that when the surface of the vitreous is observed after removal of the enveloping layers, the cells are seen without any relation to the surrounding tissues, a situation readily conducive to error. On the other hand, because of the distance between them, relatively few of the cells can be seen in histologic sections and these few may easily pass unobserved among the abundance of forms of the eye's other tissues.

As for the second factor, a reliable comparison with other parts of the body is scarcely possible, because there is no other structure like the vitreous body. A comparison, however, has repeatedly been made—though on the basis of other considerations—between the ciliary body and the choroid plexus in the ventricles of the brain; both have processes composed of a connective-tissue stroma rich in blood vessels and covered with epithelium; both form a barrier against certain substances; both produce fluids. Attention has been drawn several times to the fact that, especially near the ciliary region, the cells of the vitreous body are present in larger numbers. In this connection Kolmer's report (1921) of histiocytes in the ventricular space, localized mainly on or near the epithelium of the choroid plexus, is interesting. Kappers (1953) called these cells "epiplexus cells," because of this localization, and he was able to demonstrate the phagocytizing power of a number of them after an intraventricular injection of India ink. In the case of the cells in the vitreous body, too, most factors seem to favor the view that they should be considered histiocytes, although the vital colorability and the response to India ink have not yet been established.

The present investigations, which were prompted by the facts just mentioned, consisted of a study of teased preparations and sections of normal animal eyes, and of experiments with vital dyes and India ink designed to determine the vital colorability and the phagocytizing power of the cells in the vitreous, in comparison with these qualities in the epiplexus cells.

The cells observed in these studies are undoubtedly identical with those described in the literature: the polymorphy, the cytoplasmic granules, the shape of the nucleus, the localization and distribution along the periphery of the vitreous agree well with the findings of other authors. The factors influencing the localization and distribution are unquestionably complicated. It seems probable that the almost exclusive localization of the cells in the extreme periphery of the vitreous is due to the fact that the vitreous provides a biologically unfavorable environment for the cells. The same circumstance may explain their sometimes peculiarly regular distribution: since each cell needs an area of a certain diameter for living—the size of the area being determined by the need for the supply of food and discharge of metabolic products—the cells in the vitreous have to keep a certain distance from each other. Attention has several times been drawn in the literature to the fact that the cells in the vitreous seem to have a preference for regions rich in blood vessels, a circumstance that agrees well with the assumption just mentioned. Support for this point of view has also been provided by many of the findings in this study. Certain questions, however, *e.g.*, the differences in the average numbers of cells and in the distribution that exist between different animals, still require explanation. Possibly a careful examination of the mode of vascularization will reveal the causes of these differences. It should be kept in mind that the proximity of the cells to the vessels may very well point to an ontogenetic relation between them. In that case, if cells are found at a relatively great distance from any vascularized tissue, it would seem to show that the cells are capable of movement.

The response of the cells to vital dyes, resulting in an increase of their number and, after the breaking down of the hemato-ocular barrier, in storage of the dye was obvious. The rise in the number of the cells can only be explained by the influence of the vital dye, although the cells were only faintly colored. Apparently the small amount of dye that passes over the barrier is enough to produce cellular response but not enough for visible storage. The power of phagocytosis is demonstrated by the use of India ink.

The points of resemblance between the cells in the vitreous and the epiplexus cells can be summarized as follows: (1) both are situated behind a barrier; (2) both lie preferably in close proximity to blood vessels; (3) the preferred site of the cells in the vitreous is the ciliary body and of the epiplexus cells, the choroid plexus—two structures that have much in common morphologically and physiologically; (4) in albino rats, both types of cells show a rise in number after paraneural injections of trypan blue if given in frequent and high doses, although in general no visible coloration appears in either under these conditions; (5) cells in both categories are able to phagocytize particles of India ink; and (6) morphologically both types have much in common.

As far as can be judged, the cells in the vitreous and those in the ventricles

of the brain have the properties of the group called histiocytes. Like the cells in the vitreous and the epiplexus cells, the histiocytes are more numerous in the neighborhood of blood vessels. They have been divided into several groups, some having the power of phagocytosis and storage of vital dyes. From the author's experiments with vital dyes, it seems evident that the cells in the vitreous originate from the adventitial cells of the papillary vessels, from the ciliary body, and most probably from the retina. Thus these findings are largely in agreement with those of Schwalbe (1874). Special interest attaches to the fact that these sites have often been described as the source of infiltrating cells in pathologic and experimental conditions.

As to the function of the cells in the vitreous in physiologic circumstances, little can be said. It may be that they have the task of clearing away metabolic products, or that they take part in the maintenance of the hemato-ocular barrier. The opposite view, formulated long ago but recently brought to the front in a modern form by Szirmai and Balazs (1958), is that they take part in the anabolism of the vitreous substance, most probably in the production of hyaluronic acid. Indeed, the histiocytes have been mentioned as the possible producers of mucopolysaccharides, but this assumption is still unproved.

In connection with the hemato-ocular barrier, the author's findings are in agreement with those of earlier workers, who found that in the newborn organism the cells in the vitreous are colorable with vital dyes as a result of the fact that the barrier is not yet fully developed. In the full-grown organism the optic disk appears to be a place of minor resistance in this barrier, for if stained cells are found at all, most of them lie in the neighborhood of the optic disk. Moreover the internal limiting membrane of the retina apparently forms part of the barrier, because dye brought into the vitreous space can only reach the retina in cases of retinal perforation or inflammatory reaction.

Comment: The paper gives an extensive and thorough summary of the literature available on the cells of the vitreous body from as far back as 1840, when Hannover first described these cells.

The experimental material presented is partially a reconfirmation of previously described data, such as the distribution of the cells on the surface of the vitreous body and their apparent relationship to the retinal vessels in cattle, and the morphology of these cells as seen in phase-contrast microscopy or after staining with cationic dyes. On the other hand, some of the observations made by the author present new evidence for the phagocytic activity of these cells. Experiments with vital dyes and India ink seem to support previous findings that these cells behave like phagocytes when this material is administered locally, but not when it is administered systemically.

A very interesting aspect of these experiments is the correlation of the behavior of the vitreous cells with the cells of the epiplexus in the ventricles of the brain. The similar behavior of these two types of cells indicates the presence of a similar blood tissue barrier.

To the less convincing experiments of this work belong the cell counts of the vitreous body of the ox, pig and cat. Without sufficient statistical data and without reasonable assurance that the surface of the vitreous did not undergo shrinkage under the condition of cell counting, the figures given can only be regarded as approximate. Consequently, the differences in the number of cells counted on the surface of various parts of the vitreous body cannot be evaluated.

Statements about the motility of these cells in the surviving preparations are also quite inconclusive, and since these experiments were made, it has been shown conclusively by microcinematography that these cells show very active motility (L. Toth, E. A. Balazs, E. A. Eckl, Cinephotomicrographic studies on the cells of the cortical layer of the vitreous body. XVIII International Congress of Ophthalmology, Brussels, September 8–12, 1958).

The reviewer agrees with the author that it is probably safest at this time to refer to these cells, which are connective tissue cells but probably not fibroblasts, as histiocytes.

ENDRE A. BALAZS

THERAPEUTICS

OBSERVATIONS ON THE USE OF UREA IN RHESUS MONKEYS

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The effectiveness of urea in lowering intracranial and intraocular pressure was demonstrated in 400 patients. The majority received this agent intravenously in 30 per cent concentration. The purpose of the present investigation was to ascertain the following points: (1) the optimum rate of administration of lower concentrations of urea; (2) the most desirable vehicle for the administration of urea; and (3) effect of subcutaneous injections of urea.

Adult, female Rhesus monkeys (average weight, 4.5 kg.) were used. In the first group cerebrospinal fluid pressure measurements were carried out. In the second group, blood and urinary studies were carried out before and at frequent intervals after the urea administration. In the third group, intraocular pressure measurements were obtained every 30 minutes with the monkey in the supine position using a McLean tonometer.

Although repeated injections of 30 per cent urea could bring about satisfactory levels, this did not seem desirable because of multiple venous punctures. It was also hoped that one might be able to administer 5 per cent urea solution as a substitute for fluid intake during the period when control of increased intracranial pressure is necessary. It was observed that when urea was injected slowly the cerebrospinal fluid pressure rose, whereas, when it was administered rapidly, the pressure fell.

As to the most desirable vehicle, a combination of 30 per cent urea and 5 per cent dextrose in water was used. This was well tolerated with the exception of occasional hemoglobinuria. In search of an ideal solvent, the authors used a series of 11 vehicles for the 30 per cent urea solutions which were tested in Rhesus

monkeys. For all practical purposes, the 10 per cent invert sugar and 5 per cent dextrose in water are equally desirable, 10 per cent invert sugar having a slight advantage for the lack of occasional hemoglobinuria which was observed with 5 per cent dextrose in water.

All monkeys tolerated the subcutaneous injections well and there was no necrosis or sloughing of skin at the site of injection. Urea was found to be effective in lowering both the intraocular and the cerebrospinal fluid pressures, although not to the extent achieved by the intravenous route. The efficacy of subcutaneous administration was increased by the use of Alidase and a slower rate of injection. Clinically, the authors' experience with subcutaneous injection of urea is limited. It should, however, be pointed out that although higher concentrations of urea are tolerated in monkeys they may prove harmful in man. The authors have not used concentrations higher than 10 per cent in man and are hesitant to do so. In any case, only occasionally will the subcutaneous route have to be resorted to. Their studies, to date, would indicate that the subcutaneous route may be useful, but further investigation is warranted.

(*See editorial comments following next article.*)

UREA—NEW USE OF AN OLD AGENT

Reduction of Intracranial and Intraocular Pressure

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Reluctance to use urea intravenously in man was possibly derived from several experimental studies in dogs and rabbits which indicated that urea is toxic when injected intravenously. It is also possible that because of unsatisfactory results obtained with other hypertonic solutions, no one was sufficiently interested to give this "waste product" a fair trial.

Urea is one of the most useful nonmetabolized nonelectrolyte diuretics. The normal blood urea nitrogen level is 15 to 20 mg. per 100 ml. The indications are that 75 to 300 mg. per 100 ml. may be toxic; it should not be used if there is marked impairment of renal function. A moderate elevation of nonprotein nitrogen of the blood, however, does not contraindicate its use.

Eleven different vehicles were used in Rhesus monkeys; it was found that 10 per cent invert sugar (Travert) was the most satisfactory. This was the only combination that consistently did not produce hemoglobinuria. The combination

of urea and 10 per cent invert sugar (70 ml. of invert sugar for each 30 gm. of urea) is now used routinely in the neurosurgical service for intravenous administration. Lower concentrations of urea have also been used in the following percentages: 2, 3.3, 5, 7.5, 10, 15 and 20. Experience in monkeys tends to show that when lower concentrations are used the rate of administration should be sufficiently rapid in order to achieve a cerebrospinal fluid pressure reduction similar to that obtained with a 30 per cent solution. Urea has also been used by mouth, and in a few patients it was administered subcutaneously in concentrations of from 2 to 10 per cent, with 5 per cent dextrose in water as solvent.

After urea was proved to be a safe agent well tolerated in large doses, the dosage was increased until, today, in the majority of patients, it is 1 gm. per kg. of body weight. In many patients up to 1.5 gm. per kg. have been given and even larger doses have been used.

In the present study urea was administered to 300 patients with various types of intracranial, intraocular and spinal cord lesions. Urea was found to be a highly useful and safe agent for reducing intracranial and intraocular pressure. It is in every respect far superior to all other agents used for this purpose. The majority of the patients received a 30 per cent solution intravenously, with an average dose of 1 gm. of urea per kg. of body weight. Ten per cent invert sugar was found to be the best vehicle. The effects of varied doses of urea were compared in patients with normal and markedly elevated cerebrospinal fluid pressures. Shrinkage of brain and reduction of intraorbital volume were observed at the time of operation. Urea nitrogen levels were determined in blood, cerebrospinal fluid and urine.

A 30 per cent sterile urea solution can be prepared by adding 70 ml. of sterile 10 per cent invert sugar in water to each 30 gm. of urea crystals. The use of 10 per cent invert sugar as the solvent will avoid hemolysis of red blood cells. Only freshly prepared solutions should be used, to avoid decomposition of urea solutions due to aging. The recommended rate is about 60 drops per minute. Maximal effects will occur within 1 hour of administration. Reduction of intracranial pressure will persist for periods of from 3 to 10 hours. No complications referable to the administration of urea have been observed, but poor renal function and active intracranial bleeding should be considered contraindications. Urea is a useful and effective agent and deserves proper recognition.

Comment: One cannot help being impressed with the beneficial effect of properly administered urea on such conditions as pseudotumor cerebri; on facilitating intraorbital surgery for the removal of intraorbital neoplasms and on the preparation of the patient for operation who failed to respond to medical measures for the treatment of acute glaucoma. There is no doubt that urea, first used for reducing intracranial pressure by Fremont-Smith and Forbes in 1927, can be helpful for short-term therapy in ophthalmology as most recently confirmed by McLean *et al.* (A.M.A. Arch. Ophth., 1959). Dr. Javid's studies would indicate that a 30 per cent concentration of urea in 10 per cent invert sugar is the method of choice for administration to date. It is interesting that subcutaneous administration of urea will lower intraocular pressure. The recommended rate of administration is 60 drops per minute. One can anticipate that the maximum effect of adminis-

tration will occur within 1 hour and may persist for as long as 10 hours. Invert sugar is used as a solvent in order to avoid hemolysis of red blood cells. One should pay attention to the complications of therapy. No systemic side effects have been noted in the 300 patients reported by Javid except in one who received a total dose of 4400 mg. per kg. in 20 per cent concentration and this patient showed symptoms of dehydration which could be corrected by liberal administration of fluids. It is felt that this complication can be avoided by using smaller quantities of urea. One might see thrombosis of the vein used for injection. Various irritations of the subcutaneous tissue may appear following infiltration in this area. In patients with normal intracranial pressure, administration of urea may cause headaches similar to headache seen after lumbar puncture. There have been many attempts to use osmotherapeutic agents for the control of intraocular pressure over the course of the past 50 years. These have included sucrose, hypertonic saline, sorbitol as well as others. The current interest now resides with the use of urea which would seem to be a potentially useful agent when properly used.

IRVING H. LEOPOLD

NEW OPHTHALMIC DECONGESTANT, TETRAHYDROZOLINE HYDROCHLORIDE: CLINICAL USE IN 1,156 PATIENTS WITH CONJUNCTIVAL IRRITATION

HAROLD C. MENGER

Brooklyn, New York

J. A. M. A., 1959, *170:* 178–179

Nonspecific local preparations in the management of conjunctivitis should ideally have the following features: (1) optimum activity at low concentration; (2) few or no side effects; (3) prolonged stability; and (4) no masking or increased likelihood of secondary infection.

Preliminary observations on tetrahydrozoline (Visine hydrocloride, Pfizer), a unique pressor amine, indicate that it has optimum activity at a low concentration, 0.05 per cent. It was evaluated thoroughly in the short-term and long-term management of 1,156 patients with conjunctivitis of varying etiology. Seventy-one children, aged 3 to 12 years, and 1,085 teenagers and adults, aged 12 to 91 years, were included in the group.

Tetrahydrozoline hydrochloride is a sympathomimetic agent which causes local vasoconstriction when topically applied and a rise of blood pressure when given systemically. Instilled as a 0.05 per cent solution, it was found to afford prompt relief, lasting from 1 to 4 hours, from the congestion accompanying allergic or chronic conjunctivitis. It was administered in doses of a single drop instilled into each eye two to four times daily. This dose, although sufficient to give the desired relief in the majority of patients, had no side-effects beyond a mild, transient irritation. The intraocular pressure was not raised, nor were

adverse effects observed in its use for periods up to 2 years in patients with cataracts. No evidence was found that it affected the course of cataract or hindered recovery from chronic conjunctivitis or from the subacute stage of acute conjunctivitis.

To determine the effect on intraocular tension, over 100 patients with cataract received tetrahydrozoline daily for a period exceeding 2 years; intraocular tension was determined periodically by means of the Schiötz tonometer.

Of 348 patients with allergic conjunctivitis included in the present study, 271 concurrently received antihistamines orally to help control other symptoms. The therapeutic efficiency of tetrahydrozoline was somewhat enhanced, as might be expected, by the simultaneous adminstration of antihistamine agents. Without antihistaminic therapy, the administration of tetrahydrozoline produced a good effect in 43 of 77 patients, fair in 29, and it was ineffective in 5 patients. With antihistamines, it effected a good result in 190 (70 per cent) of 271 patients, fair in 74 (27 per cent) and poor or no result in 7 patients.

In chronic conjunctivitis, good responses were seen in 73 (64 per cent) of 116 patients with acute conjunctivitis in the subacute stage; the effect was fair in 38 patients (32 per cent) with this indication, and 5 did not respond. Patients with nonspecific conjunctivitis with hyperemia responded almost equally well.

In no instance did intraocular tension increase. None of the ophthalmic reflexes appeared to be impaired by the prolonged use of the drug, and there was no apparent change in pupillary size. Twenty-five patients (2.1 per cent) reported a mild stinging sensation with instillation; this effect dissipated rapidly. In no instances were rebound phenomena observed. In two cases, where a mild subconjunctival hemorrhage occurred, this effect may have resulted from trauma due to rubbing the eyes. The incidence of secondary infection in the series was not materially different from that expected in any random series of patients; thus, the drug was not thought to reduce local tissue resistance.

Treatment with tetrahydrozoline hydrochloride ophthalmic drops provided effective decongestant action in 96 per cent of the patients with allergic conjunctivitis and 89 per cent of patients with various forms of chronic conjunctivitis.

Comment: The sympathomimetic agent, tetrahydrozoline hydrochloride, has been used in a large series of patients over many months to 2 years. It seems to bring about relief of symptoms, particularly those due to allergic conjunctivitis. It has been observed that the intraocular pressure did not increase in any of the individuals. Unfortunately, the report does not include a summary of the influence on intraocular pressure readings nor is there any indication of what this drug is doing to the facility of aqueous outflow or aqueous formation. There is no recording of any changes of the systemic blood pressure readings following the prolonged administration of this drug. The authors call attention to the fact that the drug can raise blood pressure when given systemically. Certainly the drug appears to be safe from the aspects of lowering tissue resistance. One cannot anticipate that this drug has any influence on the bacterial flora but the data does not confirm this one way or another. In eyes in which infections were suspected as being present, antimicrobial agents as well as corticosteroids had been used along with tetrahydrozo-

line. Therefore one cannot be certain that this agent might not have had a deleterious effect on infectious processes if used alone although there is no reason to believe that it would. This appears to be a useful agent for patients with external allergic manifestations, particularly as it does not seem to predispose to fungal infections and overgrowth of other organisms. This might be a drug to consider, along with epinephrine, privine or phenylephrine in proper concentration, for the therapy of these conditions rather than corticosteroids. It might be helpful to know how this agent influences epithelial regeneration, the components of the tear film and viral keratitis.

IRVING H. LEOPOLD

VITAMIN B_{12} AND THE COURSE OF DIABETIC RETINOPATHY

HARRY KEEN AND REDMOND SMITH

Lancet, 1959, *1:* 849

The possible influence of vitamin B_{12} on the course of diabetic retinopathy was studied in a controlled clinical trial. By means of maps, the microaneurysms, hemorrhages, and exudates observed in a selected segment of the retina were recorded at bimonthly examinations over a period of 1 year and were analyzed statistically for density, change, and activity. Vitamin B_{12}, 150 μg. daily, given by mouth to 12 patients, gave them no advantage over 13 controls. The study provided evidence, however, of the dynamic nature of the lesions and led to the conclusion that in the early stages the pathologic process is probably reversible.

Although this study failed to show an effect of vitamin B_{12}, the method used gives a valid assessment of a therapeutic effect and promises to provide new knowledge concerning the natural history of diabetic retinopathy and its pathogenesis.

Comment: As anticipated from many previous reports on the failure of large doses of parenteral vitamin B_{12} to alter the course of diabetic retinopathy, the present study confirms the lack of effect of oral vitamin B_{12}. It casts further doubt on the optimistic recent report by other British investigators (A. J. Cameron, and G. J. Ahern, Brit. J. Ophth., *42:* 686, 1958; see SURVEY, *4:* 520, 1959). A side-light of the present investigation was the authors' recognition of the well known variability of the picture of diabetic retinopathy. Spontaneous exacerbations and remissions characterize this disease process even on no therapy. This point needs constant re-emphasis especially when attempts are made to evaluate newer forms of treatment.

BERNARD BECKER

STERILE EYE DROPS

Brit. M. J., 1959, *April:* 1028

Infection carried to the eye from drops used in ophthalmic out-patient departments is a chronic problem with acute recrudescences. Much ingenuity has been spent on producing drop bottles and methods of dispensing drops that would prevent outbreaks of infection, but it has become increasingly clear over the years that all ophthalmic drops are prone to become infected in one way or another. The only safe procedure is to use drops that are self-sterilizing. In practice this means the addition of carefully selected and tolerated antiseptics, for it must not be assumed that even an antiseptic solution will of necessity be sterile. In fact, penicillin drops are often grossly contaminated by organisms insensitive to penicillin.

In 1955 a special committee was set up at Moorfields Eye Hospital to study the problem, and its report, recorded by Mr. Frederick Ridley,[1] helps to clarify the difficulties. It was found that practically all the drops employed at the hospital, including many in bottles that had not been opened, were infected, and that infection by *Pseudomonas pyocyanea* was particularly apt to occur. Antibiotics in strengths commonly used in ophthalmology offered no effective protection against such contamination. Care in the use of drops—such as preventing the dropper from touching the eye or the neck of the bottle—is obviously not very effective. Drawing on the work of M. Klein and his associates,[2] the committee found that 0.004 per cent phenylmercuric nitrate and 0.1 per cent methyl hydroxybenzoate are the most generally useful protective agents to be added, the first being less irritating and probably more widely effective. It appears that efficacy does not set in until 3 hours after the addition of the agent.

As to the bottles themselves, the orthodox Chalk's bottle has been discarded in favor of screw-cap bottles provided with a plastic collar and a rubber unit carrying the glass dropper and rubber teat. It would seem that, with commonsense precautions and avoiding the use of the same pipette more than once, such bottles, with the screw cap and rubber unit removed, can be used in the operating theater with safety. Apparently there is no objection to employing the dropper from the drop bottle repeatedly in the out-patient department except for infected cases. The use of oily drops has been abolished, as they cannot be effectively sterilized. Ointments are dispensed in sterile tubes. For special purposes, such as contact-lens solution possible contamination is countered by the use of 0.2 per cent chlorbutol; stronger concentrations of chlorbutol cause deposition of needle-sharp crystals. For treatment in the wards it is considered that each patient should have his own supply of drops. Development along these lines has proved effective at the two branches of Moorfields Hospital. For the past three years repeated tests of trial bottles have all proved sterile.

REFERENCES

1. Ridley, F., Brit. J. Ophth., 1958, *42:* 641
2. Klein, M., Millwood, E. G., and Walther, W. W., J. Pharm. (Lond.), 1954, *6:* 725.

Comment: Sterility of eye drops depends on three principal factors: (1) sterile preparation (2) preservation against growth of bacteria and fungi, and (3) aseptic handling. The effectiveness of these techniques is evidenced by the fact that during the past 6 years cultures of over 1,000 bottles of ophthalmic medications in use at the Massachusetts Eye and Ear Infirmary have revealed only one instance of contamination.

We do not agree with Mr. Ridley that there is no objection to using the dropper from the drop bottle repeatedly in the out-patient department. Thygeson has cited instances in which 20 or more cases of epidemic keratoconjunctivitis were traced to a single bottle of tetracaine hydrochloride. For this reason we insist upon the use of a sterile intermediary dropper which is discarded after a single use. Only in the case of an individual patient's medication do we approve of dropper-top or "squeeze" bottles.

Although other preservatives may be almost as effective, we prefer the use of 0.5 per cent chlorobutanol and can report no complications during the 30 plus years in which it has been used almost exclusively in our hospital. (It is of interest that the single instance of pseudomonas contamination was in a bottle containing Zephiran and not chlorobutanol.)

For irrigation of injured eyes the use of individual units of chlorobutanol-preserved saline is recommended even if the injury is no more than a corneal abrasion or the bed of a corneal foreign body. These units are autoclaved in the final container (a 30 cc. soft glass bottle sealed with a screw cap containing a rubber liner) and are opened as needed and then discarded.

For treatment in wards and private rooms we are in agreement with Ridley that each patient should have his own supply of drops. To avoid mixing, these are kept at the bedside and are not returned to stock after the patient leaves the hospital.

HENRY F. ALLEN

SURGERY

PLASTIC AND RECONSTRUCTIVE SURGERY OF THE CONJUNCTIVA

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New York, New York

Plast. & Reconstruct. Surg., 1959, *24:* 1–12

After injury, surgical operation, or disease, the conjunctiva often develops more or less extensive symblepharons which may limit the size of the cul-de-sac or interfere with the rotation of the eye. If a symblepharon is not too large, it can sometimes be repaired by using flaps from the conjunctiva or vascularized tissue that covers the cornea of the affected eye itself. If, on the other hand, the symblepharons are extensive and the resulting contraction of the conjunctiva is pronounced, there may not be enough tissue in the affected eye to correct the defect without leaving bare the areas from which the flaps were dissected. In such cases, the bare areas have to be covered by material from another source. On the whole, therefore, the graft material best suited for the repair of an eye which has preserved vision is the buccal mucosa. Such a graft covers the defect in the eyeball better than do flaps of conjunctiva from the same eye or free conjunctival grafts from the other eye. Unless the defect is very small, conjunctival flaps from the same eye may contract and the pterygium recur and cause an increased amount of scar tissue beyond its original border. Free conjunctival grafts from the other eye cause unnecessary scarring of the healthy eye.

The objection that buccal mucous membrane grafts remain thick and unsightly does not hold true if the graft is thinned down enough so that it consists only of epithelium and a minimum of supporting tissue; a thin buccal graft should be almost indistinguishable from the surrounding conjunctiva. Careful anchoring of the graft (whether a conjunctival flap or buccal mucous membrane) is essential to prevent contraction and to minimize scarring. Dissection of a buccal mucosal graft can be facilitated by the use of the author's electrokeratome and two new clamps devised by him, one to pull forward the edge of the lower lip, and the other to provide exposure of the inside of the cheek when additional material is needed for a graft. More than enough material, however, can usually be obtained from the inner part of the lower lip. One great advantage of the electrokeratome over previous methods of dissecting buccal mucous membrane grafts is that it cuts the grafts so thin that further thinning is not needed. In addition, the buccal area from which the graft is taken does not need to be sutured, but is epithelialized within a few days. The patient suffers little discomfort and the lip is left with no trace of the dissection, or at least with an area of cicatrization which is unnoticeable. The area of the limbus involved in the dissection of symblepharons and pterygiums is treated with β-rays to prevent revascularization.

Various cases illustrating the author's instruments and technique and the results obtained by their use are presented in the original article.

A STUDY OF MORTALITY RATES DURING GENERAL ANESTHESIA FOR OPHTHALMIC SURGERY*

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Am. J. Ophth., 1958, *45:* 847–849

A survey of the experience of 577 ophthalmologists demonstrates that there is an anesthesia problem in ophthalmology, that mortality is significant and morbidity is commonplace, and that these conditions exist in the largest medical centers as well as in smaller institutions.

In August, 1956, a questionnaire was sent to 922 ophthalmologists, for which every fourth name from the list of diplomates in ophthalmology was selected. There were 577 responses; it was decided to use only the figures for the last 10 years. During the period from 1946 to 1956 there were 72 deaths from surgery under general anesthesia. This extrapolates to 456 deaths among all diplomates, an average of 45.6 per year. There are, without doubt, many more mortalities in the large groups of noncertified ophthalmic surgeons, including practitioners and residents.

The age range of fatalities was from 5 months to over 70 years, but the largest number of anesthetic deaths occurred in children up to the age of 9 years. This study was not conducted in a manner that permits valid detailed statistical conclusions. However, the ophthalmic surgeon rarely has the problem of an acutely ill and debilitated patient who requires an emergency operation. Most ocular surgery is elective and many operations on children in apparently good health are for strabismus. Here the rate of mortality is almost unbearably great.

The authors believe from their experiences and those related by others that the mortality in ophthalmic surgery is far higher with general than with local anesthesia.

Comment: One interesting part of this article lies in the age range of fatalities. The range was from 5 months to 70 years, but the largest number of deaths occurred in children up to 9 years of age, with half of the total number of deaths below 7 years of age. General anesthesia was the method used in these patients.

It is stated also that endotracheal intubation was the most frequent technique employed for the administration of anesthesia and that ether was the most commonly used agent. The use of muscle relaxant drugs in the age group below 7, where most of the

* From the Survey of Anesthesiology, *3:* 544, 1959.

deaths occurred, seems unlikely because these patients are intubated so easily just using ether anesthesia. Therefore, the causes of the mortality must lie in faulty endotracheal technique. Kinking of the tube, improver removal or failure of removal of secretions will result in respiratory obstruction. Partial obstruction can also be the result of the tube being advanced too far so that it enters one of the main bronchi or obstructs air entrance into one of the main bronchi. Deep ether anesthesia and respiratory depression from muscle relaxants (when used) should be recognized readily and corrected early. Partial respiratory obstruction from whatever cause may not have been considered by some as being too important until the blood pressure began to fall as the result of hypoxia and hypercarbia. The combination of hypoxia and hypercarbia, if prolonged, will produce shock that resusciatative measures will not correct.

Kirsch *et al.* (Arch. ophth., *58:* 348, 1957) have reported on electrocardiographic changes during ocular surgery. These changes were thought to be due to an oculovagal reflex initiated by manipulation of the extraocular muscles, causing first a bradycardia which may progress to cardiac arrest. If bradycardia develops during ophthalmic surgery in the presence of a patent airway and a comparatively light plane of anesthesia, oculovagal stimulation should be suspected, especially if the bradycardia is relieved by discontinuing pressure or traction on the extraocular muscles. Retrobulbar injection of procaine will obtund the reflex completely so that surgery may progress without further difficulty.

ROBERT L. PATTERSON, M.D.

WOUND HEALING

II. An Evaluation of Surgical Suture Material

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Surg. Gynec. & Obst., 1959, *108:* 555–566

The ideal surgical suture would consist of material which would permit use in any operation, the only variable being the size as determined by the required tensile strength. It should handle comfortably and naturally to the surgeon. The tissue reaction stimulated should be minimal and, above all, should not create a situation favorable to bacterial growth. Tensile strength should be high in small caliber. A knot should hold without fraying or cutting. The material should be easy to thread and not shrink or fray. It should be nonelectrolyte, noncapillary, nonallergenic, and noncarcinogenic. The suture should be inexpensive. Sterilization should be accomplished easily by boiling or autoclaving without alteration of the suture. The material might also be absorbed with minimal

tissue reaction after it has served its purpose. Obviously, this ideal surgical suture material is not available.

The studies reported in the present paper were carried out in order to compare surgical suture material by four criteria: tensile strength of the wound, histologic study of the wound, change in tensile strength of the suture, and histologic grading of the tissue reaction to the suture. The following sutures were studied: no. 4-0 chromic catgut, no. 2-0 chromic catgut, no. 2-0 plain catgut, no. 4-0 silk, no. 2-0 silk, no. 1 silk, no. 4-0 cotton, Dacron, Teflon, nylon, Nymo, ramie, and no. 32 stainless steel wire. New Zealand rabbits of 6 to 7 months of age were used. All operations were done with the usual aseptic technique.

The above suture material was studied in these animals from the standpoint of tensile strength of the sutured rectus wound, histology of this wound, tensile strength of the implanted suture loop, and grade of tissue reaction to the suture. The catgut sutures were similar to the nonabsorbable sutures until absorption began. At this time, the tissue reaction increased and the tensile strength of the suture fell rapidly. The synthetic sutures, and particularly Teflon, caused little tissue reaction and maintained tensile strength well. The tendency for the knot to slip and untie was a disadvantage but the other favorable characteristics were so decisive that alterations should be sought to produce a dependable knot.

As the Teflon was a twisted suture, fraying was very noticeable. The outstanding disadvantages of all of the synthetic sutures were the tendency for a knot to slip and the untying of the sutures in the tissues. A knot of 2 squared loops slipped invariably and of 3 squared loops, frequently. At times, even 4 squared loops would slip. The latter knot would frequently be untied by the 7th and almost always by the 14th postoperative day. It was estimated that one loop untied every 2 to 4 days.

A braided suture rather than twisted would probably decrease the amount of fraying.

A total of 287 animals was studied, which provided 842 wound tensile strength determinations, 745 suture tensile strength determinations, and 272 wounds and 1,179 sutures for histologic grading. The catgut sutures maintained their tensile strength well through the 14th day but by the 42nd day had lost considerable strength. Silk, cotton, Dacron, and Teflon lost very little strength during the period of observation. Nymo and nylon showed very similar curves of decrease. Ramie lost strength rapidly after the 14th day. Histologically, the reaction to all of the sutures after implantation for 2 days was very similar. The reaction consisted mainly of red cells, fibrin, and a few white cells, a degree of response which may be anticipated if only a needle and suture are passed through tissue. After the 7th postoperative day, the reaction to the absorbable and nonabsorbable sutures differed appreciably. The latter uniformly showed mature fibrous tissue with an inner layer of younger fibrous tissue cells. The absorbable sutures showed the same reaction until absorption began. At that time, the acute inflammatory cells returned.

POSTOPERATIVE WOUND INFECTIONS

EDITORIAL

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A. M. A. Arch. Surg., 1959, *79:* 141

Judging from current literature and discussions at medical meetings, postoperative wound infections are becoming of sufficient frequency and seriousness to justify everyone's attention. Altemeier in his recent report to the Governors of the College of Surgeons covered the subject very completely. He decried the widespread use of antibiotics for conditions for which they have been proved to be of no specific value. The common cold, I believe, is one of the best examples. Prophylactic use of antibiotics in clean surgical cases should be discontinued.

All hospitals should have a committee to investigate means of prevention as well as to investigate wound infections when they occur. It is better to prevent such infections by rigid observation of recognized methods than it is to try and eradicate such antibiotic-resistant bacteria from hospitals once they have become firmly entrenched.

It seems generally agreed that the increased incidence of infection has resulted from increasing resistance of bacteria to antibiotics, staphylococci in particular, and in a general let down in aseptic and antiseptic techniques. It is the latter problem which I wish to discuss briefly.

Some observers believe that these organisms have not increased in virulence. If virulence has not increased and the incidence of postoperative infections have increased over that of the preantibiotic era, one can only conclude that our aseptic surgical techniques have undergone deterioration. That this has occurred has been evident to me for several years. Observations in surgical clinics over the various parts of the mainland United States and in other countries, as well as contact with the house staffs of our local hospitals, recruited from widely dispersed medical centers, lead me to believe that many of the principles laid down by Lister and others, regarding asepsis and antisepsis, are being sadly neglected.

Entirely too much reliance is being placed on the protection expected from antibiotics and the direct action of other antibacterial agents. Frequent inquiry of recent graduates as to their knowledge of Lane technique, which was widely used in operations on bones and joints (so susceptible to infection, in earlier years), reveals complete ignorance of this subject. I am sure only we of older vintage have ever witnessed an operation done in which no part of any instrument or other foreign body introduced into a wound had been touched by any object after sterilization. Such rigid technique may not be necessary today, but it certainly instilled into the operating team a surgical reflex one now sees so frequently neglected.

Some of the points of surgical technique that seem important to me, and which are frequently observed to be violated by nurses and physicians alike are as follows:

1. A three-minute or less handscrub using some preparation of hexachlorophene of varying strength is accepted by many as being sufficient. While it is true that some persons can accomplish more in one minute with a brush than others do in many minutes, I still believe mechanical cleansing of hands by initial scrub of ten minutes should be insisted upon. One should always remember that the donning of sterile gloves is no excuse for inadequate hand preparation. Too many holes occur in gloves during the course of an operation to justify such lack of care.

2. While there is no standard method of preparing an operative field, mechanical cleansing of the area seems the most important to me, and the type of antiseptic used is probably of only secondary importance. More attention to this phase of the operation needs emphasis.

3. It was the teaching some years ago that skin harbored bacteria and that it should be excluded from the operative field. In more recent years, this teaching has been largely disregarded. Large areas of skin are frequently left uncovered. Viscera are spread out over the skin with abandon. Sutures are dragged across this area, and the gloves of the surgeon and those of his assistants meet skin under the friendliest of terms. Some surgeons, after the operation is well under way, cover the skin in a desultory sort of fashion—too late and too incompletely to be of much value. I have been told that once skin drapes become wet, they are more detrimental than useful. So far I do not know of any convincing proof to show that such is the case. If it is, there are methods of protecting the skin by drapes impervious to moisture.

4. Even though the intestinal contents can be largely sterilized with adequate administration of antibiotics preoperatively, one should be careful to prevent soiling of the operative field from this source. Soiled instruments, abdominal pads, gloves, and other contaminated material should be discarded promptly. Many nurses seem inadequately taught how to keep contaminated instruments quarantined from the main source of supply. It is well to remember that a wound may be able to resist a small amount of exposure to contaminated material, but unable to resist larger amounts.

5. Speed in performing surgical operations was once thought to be the mark of a good surgeon. With good anesthesia and other supportive measures by which the patient can be surrounded, speed has assumed much less importance. There has been a tendency in some quarters, I believe, to err in the opposite direction. No one should ever sacrifice safety for speed, and neither should an operation be prolonged unnecessarily by dillydallying. Trauma to tissues and overlong exposure to sources of contamination have long been recognized as fruitful avenues of infection. With the high cost of operating room care, the economic factor, if no other, should be considered.

6. Another source of wound infection, which I believe is of great importance, is the handling of infected material by doctors and nurses alike with the unpro-

tected hand. Certainly it is better to keep one's hands free of infectious organisms than it is to try to eliminate them by scrubbing and application of antiseptics. It has been pointed out by some that the infection rate on wards where the personnel is usually less well trained is greater than it is on floors where private patients are cared for by the more experienced.

7. The importance of screening personnel with infections from the operating room seems less well recognized than formerly. Persons with furuncles and throat infections, and carriers of pathogenic germs that may be identified by proper cultural methods, are still sources to be reckoned with even in this antibiotic era.

There are many sources of wound infection that have not been touched upon, but the ones mentioned seem the ones, from my observations, most flagrantly neglected. One wonders at times if aseptic surgical techniques, like the bustle and the horse and buggy doctor, have gone out of fashion.

Comment: Principles of aseptic technique apply with full force to ophthalmic surgery. The most probable sources of organisms causing postoperative endophthalmitis are (1) the patient, especially his conjunctiva, lid margins and lacrimal passages, and (2) the members of the operating team, especially their upper respiratory and bodily cutaneous flora.

The principles of degerming the skin are well set forth by Blank *et al.*, A study of the scrub, Surg. Gynec. & Obst., *91:* 577, 1950. If the conjunctiva and lid margins harbor pathogens (as they do in 10 to 12 per cent of all clinically "clean" cases) these must be eradicated before surgery as no amount of irrigation will eliminate them at the time of operation.

Most dangerous of all medications is the solution of electrolytes used to irrigate the anterior chamber at the time of surgery. Individual 500 cc. units, autoclaved in the final container, are acceptable for this purpose.

Factors contributing to the likelihood of infection include (1) extracapsular extraction, (2) operation on the second eye during the same hospital admission, (3) a second operation on a previously operated eye, and (4) prolonged operating time. Only under these circumstances does the use of systemic antibiotic prophylaxis appear justifiable.

The surgeon who, with a minimum of talking, bustle and confusion, deftly and swiftly performs an intracapsular extraction or filtering procedure on a patient who has no pathogens in his conjunctival sac, has less than one chance in about 5,000 of encountering postoperative endophthalmitis.

HENRY F. ALLEN

EARLY TREATMENT OF ORBITAL FRACTURES

G. M. BLEEKER AND B. VAN OMMEN

Ophthalmologica, 1959, *138:* 40–53

The initial paragraph keynotes the subject of this paper by observing that many fractures involving the orbit and facial bones remain undiagnosed because of the usually alarming general picture. The diplopia may become manifest

after a few weeks but by this time it is too late for adequate treatment. Early diagnosis is stressed because the treatment of orbital fracture in the first few weeks is simple and effective.

Thorough x-ray evaluation is necessary including stereoscopic and laminographic views. The early x-ray diagnosis can be made before clinical evidence would suggest orbital fracture.

The author divides orbital fractures in three main groups, based on a correlation between the nature of the trauma, the localization of the fracture and the functional disturbances.

Group I. Fractures of zygomatic bone from frontal and maxillary bones, usually by a direct blow. The fragment is usually displaced laterally and downward.

Group II. "Blow-out fractures" fractures of the medial wall and floor of the orbit, when the orbital rim remains intact. The force being transmitted within the orbit and rupturing at the weakest point.

Group III. Injury by a pointed object resulting in fracture of a wall and roof while the orbital rim is left intact.

The author quotes Duke-Elder who sums up the situation rather well, "It is curious that it is generally considered that in a patient with a head injury fracture of the limbs can be reasonably set, while fractures of the facial bones cannot." It should be kept in mind that cerebrospinal rhinorrhoea or serious central nervous system injuries are contraindications but moderate concussion should not be a contraindication since the necessary delay means the loss of opportunity. Careful evaluation of the x-ray is emphasized and re-emphasized. The most difficult cases are those in which the ocular symptoms are not apparent in the early stages and here the x-ray picture is all important for the final decision.

Several cases are discussed from the standpoint of management. A case of fracture of the orbital rim with outward displacement of the zygomatic bone is shown. These cases are often complicated by poor closure of the lids and difficulty in chewing. A muscular imbalance should be expected due to adhesions to the inferior rectus muscle. Should a portion of the floor be involved, enophthalmos will be present. The "blow-out" fractures causing a depression of the orbital floor into the maxillary sinus will result in diplopia. This may also extend and break into the ethmoid cells. The author believes the subsequent diplopia is due to a change in position rather than muscle involvement. Damage to the lacrimal sac and the infraorbital nerve can occur when the fracture is located in this area.

Any open wounds or even if they have been sutured should be repaired after re-opening. The author recommends this for two reasons. First, the existing wounds give access to the underlying fracture, and second, the opportunity is offered for meticulous suturing, approximating layer for layer and repositioning the tarsal plates and canthal ligaments. Several methods are reviewed for replacing the fragment beginning with large forceps and continuing to immobilization of the zygomatic bone by wiring or stainless steel screws. When the screw is used, it is attached to a plastic cap on the upper denture which offers the opportunity

of following minor adjustments by serial x-rays. In comminuted fractures of the orbital floor, the author suggests the Caldwell-Luc approach using digital replacement and fixation by tamponade. When the zygomatic arch impinges on the muscles of mastication, failure will result unless adequate elevation and fixation can be done. In smaller fractures local anesthesia is sufficient. Special emphasis is laid on early reduction to avoid facial deformity. The author believes that early repositioning of fractures of the orbital rim leave no functional disturbances and heal satisfactorily from a cosmetic point of view. He further believes that residual diplopia due to enophthalmos or scar fixation can be overcome with prismatic correction and orthoptic training. Mild muscle imbalance constitutes a reason for postponement of the muscle surgery until spontaneous improvement has been excluded. The author presents a series of pictures of similar cases treated early and late showing the advantages of early treatment.

Comment: The article is very interesting and informative. The emphasis on x-ray evaluation is most important. The diplopia, which in many instances is the result of enophthalmos, will not be manifest for several weeks after the injury. This occurs because of either damage to the globe or swelling of the lids which prevents the patient from opening the eye and therefore the enophthalmos with diplopia will not be diagnosed. This enophthalmos has resulted from very small fractures of the orbital floor and therefore should be kept in mind in all cases of so called "black eye." Early correction by a bone graft as advocated by Smith and Converse or polyvinyl sponge has given satisfactory results in our hands. Many times close cooperation between the ophthalmologist, orthopedist and neurosurgeon will lessen the delay time and allow for earlier correction.

GERARD M. SHANNON

ORBITAL AND PERIORBITAL TUMORS: INDICATIONS FOR EXENTERATION

ROBERT S. POLLOCK

California Med., 1959, *91:* 207–211

The relation of the orbit to surrounding structures makes the management of malignant tumors in this region especially difficult. Before deciding on operation, careful diagnosis is essential. Histologic examination of a biopsy specimen is primary. Biopsy of the skin or eyelids is easy, but special techniques, often major procedures, are needed to obtain the needed tissues from the sinuses or orbit. Total excisional biopsy is preferable. Frozen-section analysis is useful, but routine study of the fixed specimen is better. Roentgenograms of the orbit and nasal sinus and bones help to determine the original site of the tumor and also its extension into or beyond the walls of the orbit. Roentgenograms also help to distinguish different types of tumors; mixed tumors are often confined

to the lacrimal fossa, cylindromas usually invade bone, and adenocarcinoma is likely to invade bone widely. Clinical signs, such as exophthalmos with displacement of the globe downward suggesting tumor of the lacrimal gland, should be observed, and the orbit should be routinely palpated.

Histologically, tumors of the lacrimal glands are usually benign "mixed" tumors, adenoid cystic carcinomas (cylindromas), or adenocarcinomas. Tumors of the eyelids are usually basal- or squamous-cell types, or rarely neurogenic tumors. Paranasal tumors are often anaplastic and most frequently epidermoid.

The operation is selected as suitable treatment for the particular tumor. A large majority of patients with tumors of the lacrimal gland classed as benign or mixed, are cured by conservative local removal so long as no seeding or spillage occurs. Once these small or early mixed tumors have extended into the soft tissues, however, they are more difficult to remove and may be less uniformly benign than they appear, or than the first study suggests. Moreover, anatomic relations due to bone invasion may make conservative removal impossible. Recurrence following conservative removal of larger lacrimal gland tumors is high, and an operation for a recurring tumor is likely to be a formidable procedure. Initial exenteration therefore seems indicated. Some tumors, due to anatomic barriers or wide dissemination, are inoperable.

Cancer of the eyelids may require exenteration as it may invade the bony ridge and follow the floor of the orbit, extending at times to the ethmoid sinuses or nasal bones. Such lesions always start as small, innocent-looking lesions which have been inadequately treated or neglected.

The first step in the operation is to suture the eyelids together, following which an incision is made in the outer third of the upper lid through which to perform the biopsy and the exploration. This incision is sutured, and for exenteration a wide incision is made around the orbit to the periosteum, which is then also incised and stripped from the bone; the finger is useful for the stripping. A medium-sized curved clamp is placed deep in the orbit across the muscles, nerves, and vessels, which are then severed and the orbital contents removed. Redundant tissue is cleared, and the bony walls of the orbit and sinuses are smoothed with rongeur or curette. A spit thickness graft is used to cover the defect, and a pressure dressing is applied and not removed for six days.

Comment: The management of tumors of the lids, conjunctiva and orbit present a serious problem. The author rightfully stresses the importance of early diagnosis and adequate surgery. It has been my experience that most ophthalmologists (including myself) are not radical enough in the surgical management of this type of problem. Our training is directed toward the preservation of vision and the function of the lids and extraocular muscles. This results in an approach too conservative in many cases of malignancy about the eye, especially when the deeper structures (periosteum and bone) are involved. If possible, ophthalmologist should observe and work with plastic surgeons and others who perform radical tumor surgery. By this, I do not mean to imply that the ophthalmologist is unable to perform the surgery but rather that with few exceptions ophthalmologists will infrequently see and treat this type of patient. As in all types of surgery, procedures infrequently performed, are less well performed, therefore, consulta-

tion with a fellow physician with experience in this field may be of untold benefit to the patient.

ALBERT N. LEMOINE, JR.

EINE NEUARTIGE FISTULIERENDE GLAUKOMOPERATION

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Ophthalmologica, 1959, *138:* 54–58

The author describes a glaucoma filtering procedure. He uses a small polyethylene tube to connect the anterior chamber with the subconjunctival space. The anterior chamber is then entered, starting 2 mm. from the limbus. The author has made his own polyethylene tube from pieces of material 0.2 mm. thick. The tubes vary in length from 2½ to 4 mm. The diameter of the tube is equal to the width of the instrument used in making the scleral incision (1.5 to 2 mm.). After the tube is inserted into the anterior chamber so that it fits tightly into the scleral opening, the conjunctiva is closed with two sutures which are removed after four days.

The procedure was performed five times on three patients.

The first two patients had leucoma, secondary glaucoma and keratectasia. The first patient was an 18-year-old girl. The first attempt at insertion of the tube did not succeed because the tube did not fit tightly into the scleral opening. After the incision healed, a tube was inserted but the tension rose again above normal for the time of observation of 3 weeks. However, the eye was less painful than before the surgical procedure. The visual acuity remained unchanged (hand movements).

The second patient was a 14-year-old who already had an optical iridectomy in one eye and iridencleisis in the other. The visual acuity was reduced to counts fingers. Three separate surgical procedures were performed on one eye. A tube (polyethylene) was inserted at 12, 10 and 2 o'clock, each procedure being performed at a 3-week interval. Following each procedure the tension became markedly reduced for 9 days but then rose above normal. There was no pain, no hemorrhage and no post surgical infection. One of the tubes was removed following surgery and the lumen was found to be obstructed.

The third patient had bilateral buphthalmus. Before surgery the pressure was 40 mm. Hg. The observation postoperatively was 22 days at which time the tension was 23 mm. Hg. The author noted no major post surgical complication

in any of these cases and that the procedure could be readily repeated. There was no hemorrhage into the anterior chamber during the operation and the intraocular tension was lowered slowly because of the small incision.

Comment: For many years ophthalmic surgeons have been attempting to insert some foreign material into the eye which will guarantee permanent filtration of aqueous. Some of the fundamental problems, involved are (1) the toxic reaction produced by the implanted material, and (2) the permanent immobility of the seton postoperatively, and, of course, (3) blockage of any tube used for drainage.

In my experience, based on animal research, polyethylene is inferior to silicone rubber. The polyethylene is more apt to block off, is much harder, less flexible, and more toxic than silicone rubber. The author also makes no provision for permanent fixation of the implanted polyethylene aside from making a "tight" fit through the incision. The postoperative follow-up period was very brief and I would not recommend this procedure as described in this report. Certainly more animal research is needed before any implant surgery can be recommended.

RICHARD A. ELLIS

ALLERGY AND ANESTHESIA*

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New York J. Med., 1958, *58:* 2089–2093

The asthmatic patient may present significant problems to the anesthesiologist because of impairment of pulmonary ventilation, irritability of the bronchial tree, proneness to bronchostenosis with patchy or even massive atelectasis, and heightened susceptibility to bronchopulmonary infection. For these reasons the preanesthetic preparation of these patients, the wise choice of anesthetic, and skillful handling of its administration, as well as meticulous postanesthetic observation and care, are of importance for optimal management.

Preanesthetic preparation requires maximum improvement of pulmonary function, avoidance of anxiety and the employment of sedation. Short-acting barbiturates are distinctly preferable to narcotics, and the atropine-like agents should be used with care.

Ether is the inhalation anesthetic agent of choice. Cyclopropane should be used only with great caution, as it tends to induce bronchoconstriction. The intravenous thiobarbiturates, such as thiopental and thiamylal, are contraindicated. With appropriate precautions to manage apprehension, spinal anesthesia is satisfactory for operations which can be performed with an anesthetic

* From the Survey of Anesthesiology, *3:* 583, 1959.

level below the tenth thoracic dermatome; regional anesthesia also has its place for the asthmatic patient. It must be stressed, however, that before consideration can be given to the use of either of these techniques in an asthmatic or allergic patient, a careful history must be taken to exclude the possibility of a hazardous reaction to the local anesthetic agent.

Succinylcholine is the preferred muscle relaxant in bronchial asthma, since it is short-acting, does not in ordinary dosage release histamine, and can be controlled continuously as a dilute intravenous infusion. It is noted, however, that the antagonists to excessive effects of the relaxants are all parasympathomimetic drugs which also induce asthma and must therefore be avoided.

The asthmatic attack during general anesthesia is handled best by the introduction of ethyl ether into the breathing circuit of the anesthesia apparatus or by deepening an already existing ether anesthesia, but care must be taken to avoid circulatory or respiratory depression. Isopropylarterenol (Isuprel) may be employed by nebulization or by parenteral administration.

Bronchoscopy may be indicated postoperatively for aspiration of excessive tracheobronchial secretions or for atelectasis. In the later postoperative period the asthmatic patient must be watched carefully with regard to the development of pneumonia or other respiratory infection.

Allergic reactions to the agents used in local, regional and spinal anesthesia are uncommon, and the inhalation anesthetics are scarcely ever incriminated as allergens. Reactions may occur after injection or topical application to membranes. Procaine, in many ways the safest of local anesthetic agents, has been the cause of anaphylaxis in several well documented reports. Pontocaine, administered by injection or topically to membrane surfaces, has been incriminated more frequently in fatal episodes. Preliminary skin tests are generally of no value. Where a general history of allergy and especially of reactions to drugs or serum is present, a preliminary trial dose, either subcutaneously or as drops into the lower anterior lip fold, is a desirable precaution. If no reaction occurs in 15 minutes, the hazard of any anaphylactic reaction is minimized.

Local allergic edema due to procaine, a recently observed entity, may be diagnosed by a positive 24-hour skin test. Patch tests are diagnostic in allergic contact dermatitis due to local anesthetics.

Comment: The largest part of this paper quite rightly is devoted to the management of bronchial asthma, which is the most common and most dangerous allergy with which the anesthesiologist is faced. I cannot agree too strongly with the authors when they suggest that maximum control of the asthma before operation is essential. Adrenal steroids may be made part of this preparation, but then their dosage must be stepped up preoperatively. I fail to follow the reasoning of the authors when they stress the avoidance of atropine-like agents.

In theory, ether is the classic agent, but in actual practice an ether inhalation induction is far from desirable. Any sudden increase in the vapor strength of ether, or the excitement which may accompany a slow induction, have been known to initiate an asthmatic attack, since the stimulus is far in excess of the bronchodilator effect of the small amount of ether that has been absorbed at this stage. Basal narcosis, or even in-

duction of anesthesia with intravenous ether, has some advocates. If the patient has been premedicated adequately with antihistaminics, little difficulty should be experienced from judicious doses of sodium thiopental followed by any maintenance agent, even cyclopropane if that is desired. Promethazine (Phenergan) is particularly useful as a premedicant, since it combines antihistaminic with sedative properties. This technique makes a subsequent smooth addition of diethyl ether much more simple. It may well be that Fluothane, or the azeotropic mixture of Fluothane and ether, may entirely supersede previous anesthetic techniques in the asthmatic patient. The concurrent administration of a slow aminophylline or isoproterenol (Isuprel) drip is a wise precaution, provided it does not influence cardiovascular function adversely. Vigorous antiasthmatic therapy must continue in the postoperative period and during convalescence.

The authors have omitted entirely allergic manifestations following the injection of iodine-dyes, such as are used for intravenous pyelograms, cerebral angiography, peripheral arteriography and operative cholangiograms. These procedures are becoming more and more popular and may give rise to allergic manifestations. We have encountered no difficulty since we have added promethazine to the preoperative medication.

GORDON M. WYANT, M.D.

IATROGENIC DISEASE AND ANAESTHESIA*

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Brit. M. J., *1:* 1433–1438, June 21, 1958

Some anesthetic techniques are known to produce adverse effects in certain pathologic conditions, such as spinal analgesia in the presence of disease of the central nervous system or the use of thiopental in porphyria. More recently it has become apparent that many forms of routine medical treatment may affect the response to anesthesia. In all the instances reported in this paper the effect was to engender in patients an increase in reaction of one or other of the effects of general anesthetics.

The ganglion-blocking drugs or chlorpromazine, if given before anesthesia, increase the hypotensive action of the narcotics, and severe and even fatal collapse may follow normal doses of anesthetic drugs. This reaction applies particularly to intravenous barbiturate anesthesia, where it is difficult under normal conditions to predict the degree of hypotension that will follow injection and to adjust the dose accordingly. Anesthesia in patients who are receiving other hypotensive drugs, such as the rauwolfia or veratrum alkaloids or mecamylamine, must also be handled with special care.

Phenothiazine derivatives have been found to prolong the narcotic action of anesthetics; this effect also seems to apply to the nonphenothiazine prepara-

* From the Survey of Anesthesiology, *3:* 581, 1959.

tions used for the control of tremor in Parkinsonism, and possibly may be a side effect of all the tranquilizers. A dangerous degree of respiratory depression can result from the combination of analgesic drugs and the intravenous barbiturates. Cyclopropane administered to patients who have had deep x-ray therapy to the head and neck can have a similar effect.

Adrenocortical insufficiency due to the prolonged use of cortisone, its analogues, and corticotrophin, makes patients sensitive to the stress of surgery and anesthesia. Prolonged severe hypotension, respiratory depression and delayed recovery may follow surgical operations in such patients. Such effects respond rapidly to intravenous cortisone; however, prevention by increased preoperative dosage of cortisone and corticotrophin is preferable. Increased use of the steroids draws attention to this hazard, especially in minor cases, where one does not normally associate any risk with anesthesia. Steroid-induced primary pituitary failure may also persist for several months after discontinuance of the drugs.

The incompatibility of pitocin with light cyclopropane anesthesia and the possibility of citrate intoxication as a differential diagnosis after massive transfusion of stored blood are other problems faced by the anesthesiologist.

Rarely did the anesthetist know, in the cases here considered, of the use of various drugs before operation, or associate hypotension or prolonged unconsciousness with any form of routine medical treatment. It is hoped that the attention of medical practitioners will be focused on the fact that during anesthesia unexpected adverse effects may be produced by drugs which do not appear to have any side effects in the concious subject. Further additions to the list of drugs discussed above are to be expected.

Comment: Dundee's prophecy seems certain of fulfillment; and in fact, there were additions to the list of drugs which are employed for medical treatment but can have an adverse effect upon the patient's response to anesthesia even before the ink had dried on his paper. Pridgen has reported four cases of respiratory arrest which occurred during ether anesthesia and which were attributed to the intraperitoneal use of Neomycin; two of these patients died despite extensive and prolonged resuscitative measures (Pridgen, J. E.: Surgery, *40:* 571, 1956). Subsequent laboratory investigations have revealed that neomycin has potent neuromuscular blocking action and is capable of increasing, manyfold, the neuromuscular blocking action of both ether anesthesia and certain of the muscle relaxant drugs (Pittinger, C. B., and Long, J. P.: J. Pharmacol. & Exper. Therap., *122:* 61A, 1958). Kanamycin, a new antibiotic related to neomycin, but one which is effective in the management of resistant staphylococcal infections, also has been employed by peritoneal instillation in established peritonitis, and the possibility has been raised that in some cases it, too, may be followed by adverse respiratory effects when used in conjunction with ether or curare (Finland, M.: Lancet, *2:* 209, 1958).

A somewhat different aspect of this problem is the drug employed for medical treatment which may have an adverse effect upon the patient that is attributed to anesthesia, but actually is a toxic effect of the medical therapy itself. Perphenazine (Trilafon), for instance, can produce weird neuromuscular symptoms (Shanon, J.: Dis. Nerv. System, *20:* 24, 1959) and even clonic convulsions (Graff, T. D., Phillips, O. C., and Gentry, W. D., Jr.: J.A.M.A., *169:* 834, 1959) within hours after initial modest doses in certain susceptible individuals. One recent instance of this reaction occurred in a 22-year-old male who had undergone appendectomy under spinal anesthesia and was given a total

of 12 mg. of Trilafon in divided doses during the first postoperative day as a prophylactic measure to prevent nausea and vomiting: the patient developed torticollis and opisthotonoid spasms of the trunk that were thought initially to be a neurologic sequela of the spinal anesthesia—in point of fact, these symptoms were due to Trilafon and cleared promptly within 24 hours after withdrawal of the drug.

The organic chemists are turning out new compounds faster than the pharmaceutical houses can screen them, and the pharmaceutical houses in turn are marketing new drugs faster than the medical profession can learn the trade names, let alone evaluate the drugs clinically. The majority of these drugs will be employed in areas of medicine in which the anesthetist may have little contact with their use; some of these drugs, however, may be capable of having an adverse effect upon the patient's response to anesthesia, and the anesthetist will have to familiarize himself with all of them, including their properties and their toxic reactions, in order to be alert to this possibility. At the present rate of manufacture this is not going to be an easy task.

DAVID M. LITTLE, JR., M.D.

EXTRAOCULAR MUSCLES

STRETCH EFFECTS IN HUMAN EXTRAOCULAR MUSCLE: AN ELECTROMYOGRAPHIC STUDY

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Bull. Johns Hopkins Hosp., 1959, *104:* 174–178

In human beings, muscle action potentials were recorded in primary and lateral gazes from one horizontal rectus muscle, and the effect of passive stretch was observed. With the eyes in primary gaze, the action potentials were unchanged by disinsertion or manual pull. During agonist contraction, however, stretch of the agonist itself, the agonist or yoke muscle produced a decrease in the frequency and amplitude of the discharges. This inhibitory effect was not observed when stretch was applied to the muscles of an eye which had a previous retrobulbar alcohol injection or the involved muscle in a patient with a IIIrd nerve palsy. These results suggest that the extraocular muscles of man do have receptors which can be stimulated by passive stretch.

Eight patients were investigated. The studies in these patients, all of whom had full ocular movements, were made before enucleation of one eye. In three of these, unilateral retrobulbar alcohol injection had been performed several months previously. In the remaining patient, a recent case of IIIrd nerve palsy,

the muscle remained *in situ* and stretch was applied through a forceps placed at the insertion. A similar method of stretch was used in the normally innervated eyes of the three patients with retrobulbar injection. Under topical anesthesia (Ophthaine), a concentric needle electrode was inserted into one of the horizontal recti muscles. In those patients studied before enucleation, additional stability of electrode position was achieved by suturing the needle in place. Muscle action potentials were then led to amplifiers, displayed on the beams of a cathode ray oscilloscope, and photographed. Recordings were made with the eyes both in primary and in horizontal gaze, the latter about 30 degrees beyond the midline.

In primary gaze, neither disinsertion nor stretch produced any change in the configuration of the action potentials recorded from the same muscle. Release of muscle from its insertion alone, however, does not permit complete retraction. This fact could account for the difference between the findings reported here and those of Breinin (Arch. Ophth., 1957, *57:* 176). In his postenucleation studies electrical silence developed following complete muscle retraction.

During agonist contraction, on the other hand, manual pull of agonist itself or its antagonist exerted a demonstrable inhibitory influence on the agonist action potentials. Indeed this was the only effect and it was noted in 5 of 6 normally innervated eyes. Mechanical stimulation of stretch receptors within the extraocular muscles might be the cause of this inhibition. In support of this thesis, the results in the three patients with previous retrobulbar alcohol injection are of considerable interest. In these patients, action potentials in the contracting agonists were unchanged by stretch of any muscle in the injected eye. On the contrary, muscle stretch of the contralateral eye resulted in inhibition. Certainly some sensory neurons from the eye had been destroyed by those injections, as judged by a definite depression of corneal sensation in all three patients. The absence of inhibition, therefore, might well have been caused by similar damage to afferent fibers from the muscles; this cannot, however, as yet be substantiated histologically. The fact that no inhibitory effects were obtained from the patient with IIIrd nerve palsy when a paretic muscle was stretched, also suggests involvement of afferent neurons.

Comment: The observations of the authors support the concept of a stretch sensitive mechanism in extraocular muscle. The significance and physiologic basis of the difference in stretch effects between the primary position and horizontal gaze remain to be explained. My results were similarly negative in the primary position but since the effects of stretch were not recorded in horizontal gaze the findings cited were not seen.

At first glance the results of agonist stretch might be attributed to a changed geometry of muscle-electrode relationship. This was negated by the similar effect of antagonist or yoke stretch and the absence of effect in the injected eye.

The presence of inhibitory effects in the intact eye from passive ipsilateral stretch is counter to the findings of other investigators.

The sole effect of stretch noted by the authors was inhibition in horizontal gaze. The degree of stretch was not measured but was presumably sufficient to actuate receptors of the type described by Cooper, Daniels and Whitteridge. One might speculate that the tonic outflow to the extraocular muscles in the primary position springs from a low grade

stretch feed back loop whereas gaze innervation is concerned in a high grade stretch loop in which inhibition is paramount. Further studies are necessary to clarify the confused picture of ocular proprioceptive mechanism.

Recent animal experiments in our laboratory have pointed up the tremendously important role of the central nervous system in maintaining the tonic outflow of extraocular muscle discharge. The type and level of anesthesia also greatly affect the extraocular muscle discharge. The interplay of reticular formation and muscle end-organ must influence this activity in eye muscles as it does in peripheral muscles; thus depression or activation of the arousal centers may inhibit or restore the extraocular muscle discharge.

GOODWIN M. BREININ

PARALYSIS OF THE EXTRAOCULAR MUSCLES IN DIABETES

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A.M.A. Arch Int. Med., 1959, *104:* 318–322

The neurologic complications of diabetes have been extensively studied, especially the peripheral neuropathy, and, more recently, the disturbances of the autonomic nerve function. The less frequent paralysis of cranial nerves has aroused less interest. We are reporting three cases of paralysis of the ocular muscles seen within 5 years.

In the first case, intracranial aneurysm or neoplasm were considered as possible causes until the paralysis gradually disappeared. In the second case, an ophthalmologist called in consultation surmised that the paralysis was due to diabetes, which had not so far been diagnosed. In the third, paralysis appeared in the course of an old, poorly controlled diabetes, but slowly disappeared with other symptoms as the diabetes was controlled.

In the first two cases, the third nerve was involved but the pupil was not affected, and in the third the sixth nerve was involved. In all three the onset was quite rapid and was associated with pain. The first patient had mild diabetes which was well controlled and the paralysis improved with no change in routine. In the second case the diabetes was demonstrated only by glucose tolerance tests and was controlled by weight reduction with no evidence of glycosuria at later tests. Ellenberg has reported another case with third nerve paralysis in which this was the first sign of diabetes. In the third case with poorly controlled diabetes, the patient also had repeated episodes of peripheral sensory nerve disturbances. These, as well as the sixth nerve paralysis, cleared in 2 to 3 months.

In the literature, repeated episodes of bilateral ocular muscle paralysis in diabetes always recover spontaneously. The third and sixth nerves are most frequently affected, occasionally the fourth, and possibly also the seventh. The pupil is always spared in paralysis of the third nerve. Pain is usual and may

be severe, and it may be either local or may spread to the first or second branches of the trigeminal. Spontaneous recovery differentiates diabetic paralysis from aneurysm or neoplasm, and this syndrome clears more rapidly than other peripheral nerve neuropathies.

Diabetic ocular muscle paralysis has been attributed to lesions—possibly slight hemorrhage—in the medulla or to involvement of peripheral nerves outside the brain stem. Dreyfus, Hakim, and Adams in a post-mortem examination found a fusiform enlargement of the retrobulbar part of the third nerve in one case, which seemed compatible with incomplete ischemia, possibly due to occlusion of an artery. Fagerberg considers that diabetic neuropathy is due to specific angiopathy involving the vasomotorium, with possible influence by arteriosclerosis in older persons.

Diabetic retinopathy is usually present, and there may be other neuropathies, which help to distinguish diabetic external muscle paralysis from similar conditions due to other syndromes.

Comment: There is still much dispute concerning diabetic neuropathy and indeed, some authorities question its existence. There is, however, strong presumptive evidence that it is a definite complication of diabetes mellitus and that it can involve any of the cranial nerves supplying the extraocular muscles. This evidence is sufficiently good so that every unexplained case of extraocular muscle palsy should be suspected of diabetes. King mentions pain in the orbit as being a prominent part of the complication contrary to the findings previously reported by me. (D. Snydacker, Diabetic neuropathy as a cause of extraocular muscle palsy, Tr. Am. Acad. Ophth. & Otol., *62:* 704–707, 1958.)

DANIEL SNYDACKER

ELECTROMYOGRAPHY IN STRABISMUS

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California Med., 1959, *90:* 437–439

Electromyography in strabismus, whether paralytic or nonparalytic, offers very little practical help in diagnosis and treatment. Subjects with comitant strabismus are mostly children, unsuitable for insertion of needles into eye muscles under topical anesthesia. In an occasional case, an adult with no significant difference in electrical activity as compared with normal was noted as expected, inasmuch as extraocular electromyography reflects primarily peripheral extraocular muscle activity rather than central mechanisms; this statement is true for noncomitant strabismus also. This limits conclusions regarding more central mechanisms or etiologic factors. Thus, Breinin from a study of "A-V" syndrome,

in which he noticed horizontal recti showing innervational changes corresponding to the deviation concluded that horizontal recti must play some part in varying angle of strabismus and in surgical treatment it is advisable to deal first with horizontal muscles and then vertical. Such conclusion may be misleading, for the mere fact of increased activity of a muscle may be due to new position of the eye and gives no information as to why the eye moved. Further, horizontal recti activity to this new position during vertical movements may vary greatly between normal subjects. Fewer cases of specific neuroophthalmologic types of paralytic strabismus have been studied from which it cannot properly be inferred that the patterns observed are characteristic. At present it only confirms the presence of neuropathy or myopathy. As regards diagnosis of extraocular muscle palsy, it may be noted that relative strength of a muscle cannot be judged by amplitude of electromyographic tracing except in pronounced paralysis. Even in normal conditions amplitude may vary, depending on several factors, principally location and depth of inserted electrode.

However there are a few clinical applications of electromyography to paralytic strabismus. For example, distinction can be made between limitation of eye movement due to mechanical restriction and that due to nerve damage. It appears that ocular electromyography is the most sensitive test for response of muscles to a test dose of edrophonium chloride (Tensilon) in myasthenia gravis, it may decide the diagnosis in patients who have false negative response to other usual clinical tests. It also gives objective confirmation of overaction of a yoke muscle in a paralytic strabismus.

Comment: A more sober picture of ocular electromyography is gradually emerging after the initial enthusiasm, as is usual with all the new procedures. The authors are to be commended for boldly pointing out the little that is to be gained by electromyography in paralytic and nonparalytic strabismus, a procedure by no means painless and involving use of expensive equipment and requiring great technical skill in its operation. Unlike other workers, fortunately these authors have not lost sight of the fact that electromyogram is a reflection of peripheral muscular activity and have rightly emphasized that any explanation of central mechanisms based on this procedure is open to serious criticism.

In the reviewer's experience ocular electromyography offers no particular advantage over the usual therapeutic tests in the diagnosis of myasthenia gravis. The authors have mentioned the false negative response to the other usual clinical tests but failed to elaborate on this point. Certainly Breinen's two cases (A.M.A. Arch. Ophth., *57:* 161, 1957) do not fall into this category, as both showed improvement of ptosis on usual neostigmine and edrophonium tests. If one is particularly anxious to do electromyography, a far less traumatizing and more reliable procedure is the one as suggested by Botelho *et al.* (A.M.A. Arch. Neurol. and Psychiat., *67:* 348 and 441, 1952) in which potentials are recorded from orbicularis oculi, when it is made to contract by supramaximal stimulation of the facial nerve. "This method has the advantage of eliminating the vagaries of voluntary effort and so permits an objective analysis of the function of the peripheral nerve, neuromuscular junction and muscle."

Lastly, one cannot help questioning the practice of quoting unpublished references in support of work which is already well documented in literature.

NARENDRA KRISHNA

EXTERNAL DISEASES

SHIPYARD EYE

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Brit. M. J., 1959, *2:* 429–430

In this letter to the Editor of the British Medical Journal, Cockburn refers to certain omissions in the story of shipyard eye as described by Jawetz (Brit. M. J., *1:* 873–876, 1959; see SURVEY, *4:* 622, 1959), and undertakes to supply them. The points fall into two groups—first, the historical account of the events leading to the discovery of the causative agent, and, second, the epidemiology of the disease.

In connection with the history, it may be remembered that only one vial of the Sanders EKC virus remained after the war. Identification of this virus as St. Louis encephalomyelitis virus opened up the interesting possibility that epidemic keratoconjunctivitis (EKC) and St. Louis encephalitis (SLE) were differing manifestations of the same infection, although what was known of the epidemiology of the two made this seem unlikely. The Encephalitis Investigations Unit of the Communicable Disease Center, United States Public Health Service, which was then (1951) studying the arthropod-borne viral encephalitides, particularly western equine and St. Louis encephalomyelitis, immediately turned its attention to the Sanders virus.

First, an epidemic of EKC in a glaucoma clinic was investigated. Next, the specimens of sera collected were tested for SLE and EKC antibodies, but no antibodies against these viruses were detected. Then the one surviving vial of the Sanders EKC was investigated for possible contamination with SLE virus and it was found that not only had the two viruses been stored in the same deep freeze, but that there had also been ample opportunity for the viruses to be mislabeled. The view that the SLE virus was not related to the disease was circulated among interested persons in 1951 and published in 1954.

The interest aroused in eye infections in the Encephalitis Investigations Unit led to the recognition in 1951 of a new disease entity, labeled Greeley Disease after the town in Colorado where it was first noted. This was a disease with pyrexia, pharyngitis, conjunctivitis, and corneal opacities, and the resemblance to EKC was clearly noted at the time. In 1951 the adenoviruses had not been discovered and tissue culture was in its infancy, but the sera from the 1951 cases were saved, so that when Huebner and his colleagues discovered the adenoviruses in 1953 they were able to identify the 1951 Greeley disease as the same as their pharyngoconjunctival fever and caused by adenovirus type 3. The possibility that EKC was an adenovirus infection was immediately recognized. A search for acute cases of EKC was begun, but the disease in the United States

seemed to have disappeared, and the race to isolate the EKC virus was not won until a case was discovered in an Asian sailor in California.

The epidemiology of the disease shows that classical EKC in the United States is mainly transmitted by the ophthalmologists themselves, but this is not the whole story. The unexplained question was the whereabouts of the virus between the infrequent outbreaks. The sequence of epidemics in shipyards in the early days of the second world war would suggest a spread from Asia via Hawaii, but that does not account for the odd small outbreaks that still appear from time to time. At the conference on EKC in San Francisco in 1957, the suggestion was made that the EKC virus is a strain of the pharyngoconjunctival fever virus, arising as a result of the abnormal means of transmission from eye to eye. Such a concept would explain the sporadic nature of the epidemics and also the fact that in almost all epidemics the first cases are mild and have no corneal opacities. The epidemiology of the disease in the United States would not be basically different from that in the Orient, as claimed in the "Story of Shipyard Eye." As described there, the disease in the Orient associated with adenovirus type 8 is common in children, the symptoms being fever, respiratory symptoms, conjunctivitis, and no opacities; this is, in effect, pharyngoconjunctivitis and not EKC; 25 to 30 per cent of the population have significant antibody titers to the type 8 virus. The reason why a similar picture is not found in the United States may lie in the geographical distribution of the virus type 8, which could be basically an Asian virus which spreads to other parts of the world from time to time. However, indigenous EKC viruses in the United States possibly can arise from the types already present, for type 3 has already been recovered from mild cases of EKC in the United States and Canada. There is no good evidence at present to show that type 8 is the main virus causing EKC in North America.

One difference in transmission may be that, in Asia, flies may play a part in spreading the disease. Since these insects, particularly those sucking the fluids of the eye, are extremely troublesome at certain times of the year and since they are known to carry the agents of purulent conjunctivitis, it seems likely that they could also carry EKC viruses.

In the light of these facts, it is suggested that EKC viruses are strains of those causing pharynogoconjunctival fever selected by repeated passage from eye to eye. In the United States, these strains may arise either from existing indigenous pharyngoconjunctival infections or be exotic EKC strains imported from the Orient.

Reply to Dr. Cockburn's comments: The "Story of Shipyard Eye" was a lecture delivered in London. In my opinion it is the function of a lecture to present the lecturer's viewpoint and to stimulate the audience, rather than to review completely an entire subject. It was with regret that I omitted many important investigations in the field of epidemic keratoconjunctivitis including those by Dr. Cockburn.

I have been familiar with Dr. Cockburn's suggestion that "the EKC virus is a strain of the pharyngoconjunctival fever virus, arising as a result of the abnor-

mal means of transmission from eye to eye," implying that any type of adenovirus which sometimes produced eye disease would possibly cause EKC from time to time. Present evidence, I believe, is in direct conflict with such a view, as it indicates that unrelated outbreaks of EKC in Austria, Switzerland, Italy, Britain, Germany, United States, Canada, and Japan invariably relate the typical picture of EKC to infection with adenovirus type 8—not any other type. Only very rarely has a keratoconjunctivitis (not entirely typical of EKC) been observed with infection by other types. Furthermore, infection of human volunteers has given typical EKC only with adenovirus type 8, not with other types. During the past 2 years several indigenous outbreaks of EKC in the United States have been studied and adenovirus type 8 has regularly been isolated. Thus I am forced to reiterate my belief that at the present time adenovirus type 8 appears to be the principal, and perhaps the sole, cause of typical epidemic keratoconjunctivitis.

It remains to be seen whether the epidemiologic pattern postulated for the Orient will be substantiated by additional experimental data. The sera of patients observed by Dr. Cockburn in Ceylon with a clinical picture resembling keratoconjunctivitis lacked neutralizing antibodies to adenovirus type 8 when examined in our laboratory. Thus I cannot comment on the possible roles of flies or other vectors suggested by Dr. Cockburn.

ERNEST JAWETZ

LENS

REGENERATION OF THE LENS OF THE EYE IN THE RABBIT

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Nature, 1959, *183:* 1815

In a recent communication, Chanturishvili[1] reports his re-investigation of the detailed embryology of the lens in Amphibia and refers to work on higher forms in his laboratory at Tiflis. He and his fellow-workers, in particular Sikharulidze,[2] are of the opinion that the lens fibres are derived from cells which are neural in origin, and which require for the initiation of fibre production the products of the cytolysis of epidermal elements.

As a corollary of their view of lens development the Tiflis workers have introduced small fragments of cytolysing foetal tissues into the lens capsules of adult animals from which all easily separable contents had been evacuated. They report that whereas simple evacuation without implant is followed by very little regeneration (the familiar aphakic state following the operation of extracapsular lens extraction), the addition of the implant is followed by the regeneration of a lens nearly normal in size and structure.

On a visit to Tiflis in 1955 one of us (P. G. 'E.) was enabled, by the courtesy of Prof. Chanturishvili, to see something of this work there. Later, Prof. Chanturishvili most kindly placed at our disposal, in the fullest possible detail, particulars of the techniques employed by him and his co-workers.

At Prof. Chanturishvili's suggestion, we repeated here the experimental implantation of cytolysing foetal tissue taken from the lid commissure of a three-week embryo into the evacuated lens capsules of six normal rabbits according to the technique of Tamara Sikharulidze. We kept suitable control animals in which the lens capsule contents had been simply evacuated without implantation. This work was done because it was hoped that Prof. Chanturishvili would be able to attend the Oxford Ophthalmological Congress and to demonstrate this material of ours there. In the event, he was not able to do so, but these rabbits were demonstrated there by us in July 1958, 12 weeks after operation.

At that time there were marked differences to be seen between those evacuated lenses which had received implants and those which had not. Whereas the animals without implants showed the normal aphakic post-operative condition of collapsed and apposed capsular walls, those which had received implants showed inflated and in some cases spheroidal lens capsules, the contents and shape of which had a refractive power approximating to that of normal lens. This process of regeneration is continuing eleven months after operation.

Prof. Chanturishvili visited this Department in August 1958 and allowed us to examine his embryological preparations and generously presented us with material. He states that about 16 months are needed for full regeneration, but

our most promising rabbits have lenses already little different from the normal in size. The iris can be seen to be supported by the convex anterior surface of the lens as in the normal eye, whereas in the aphakic controls the unsupported iris presents a concave surface to the observer.

Assessment of the structural and functional state of each lens in an ophthalmological sense has been made at frequent intervals by evaluation of the refractive condition of each eye as a whole by ophthalmoscopy and skiascopy. Whereas the normal unoperated eye in our rabbits is from zero to two and a half dioptres hypermetropic, the aphakic control eyes have consistently been found to be of the order of ten to fifteen dioptres hypermetropic. By notable contrast, the eyes which had received implants have been found, in the areas of incipient lens regeneration, to be comparable in refractive power to the normal as early as eight weeks after operation.

The progressive variations in shape and appearance of the lens capsule and its contents in each case have also been surveyed by frequent slit-lamp biomicroscopy. In every lens which received a foetal implant the anterior and posterior capsule walls have become separated in part, and in some instances fully. The lens has assumed a progressively spheroidal shape. Relucence of the substance within the capsule suggests that it possesses optical properties comparable with those of a normal lens and differing from those of aqueous humour.

The approximately lenticular shape of the most successful examples and their relatively transparent and homogeneous contents make possible a satisfactory ophthalmoscopic view of fundus detail. Even in the best, however, there are some variations of optical density still remaining. These may possibly be ascribed to incomplete cytolysis of implanted material, or to incomplete removal of the original contents of the lens capsule. On the other hand, some of them may represent a stage in a process of regeneration not yet complete. Distortions of shape and incomplete separation of the capsule walls, which were found particularly in our first few operations, are probably due to faulty technique.

The preliminary observations reported here seem so far to confirm the findings of the Tiflis workers in the rabbit.

We propose to repeat our work here on a larger scale to allow the sectioning of regenerating lenses at all stages. It seems to us that this filling out of the capsule in so short a time may perhaps be ascribed to the secretion of a 'ground substance,' in which fibres may grow later, more probably than to actual immediate growth of functional fibres.

Sikharulidze reports retarded but satisfactory regeneration of lenses in rabbits after the removal of cataracts induced chemically. At present we are engaged in a repetition of our work using rabbits which have received high doses of local irradiation.

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Comment: This brief report from Hull, England, provides confirmation of one of the most exciting findings of recent years. The original work stems from observations on lens

regeneration in the amphibian eye and the induction of lenses by bringing the optic vesicle in contact with surface ectoderm. In reports from Chanturishvili's laboratory in Tiflis, the complete regeneration of the normal adult mouse or rabbit lens has been claimed. This has occurred after extracting the lens extracapsularly and implanting in the capsule degenerating embryonal skin fragments from the lid area or preserved minced mouse brain. Similar regeneration of the normal lens architecture has also been obtained in approximately one-third of cataractous lenses in mice (traumatic cataract) and rabbits (magnesium chloride injection into the lens) (Sikharulidize 1956).

The present report of Stewart and 'Espinasse not only confirms these findings in normal rabbit eyes, but even claims restoration of normal phakic refractive power, normal slit lamp appearance, and a satisfactory view of the fundus! Although one may question the rationale for the use of degenerating ectoderm as an "organizer" for the development of lens fibers, it is clear that laboratories throughout the world must make efforts to confirm or deny these most provocative observations.

BERNARD BECKER

CORNEA

PRESENT STATUS OF OPTICAL CORNEAL GRAFTS

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Henry Ford Hosp. M. Bull, 1959, *7:* 65–67

Maintenance of corneal transparency is the prime consideration in optical keratoplasty. All too often corneal transplants become clouded even when the surgical technique has apparently left nothing to be desired. Some of the factors that influence graft clarity are still obscure, but certain principles have emerged distinctly. First, the corneal conditions favoring keratoplasty seem to be (1) nonedematous "degenerations"; (2) residues of chronic infections or nonspecific inflammations; and (3) traumatic lesions. The prognosis is least favorable in edematous degeneration, whereas the most satisfactory visual results are obtained with grafts for keratoconus, a dry avascular "degeneration."

For best results, both the donor cornea and the recipient bed must be transparent. The weight of evidence supports the view that the cells of the graft are replaced by the host (epithelial cells almost immediately, stromal cells and endothelial cells very gradually), but that Bowman's membrane, the collagen framework of the stroma, and Descemet's membrane persist morphologically. Cell death occurs at a considerably increased rate after keratoplasty, but, even so, goodly proportions of the donor cells remain viable, usually for months, but possibly for years. Simultaneous death of all stromal cells in the graft does not

occur. The speed of replacement of donor stromal cells by host cells is felt to be inversely correlated with the "success" of the graft.

The orderly regeneration of normal transparent cornea can be impeded or prevented by structural and metabolic disturbances of both the recipient bed and the donor cornea. These disturbances may be brought about in at least three ways: (1) immunologic response of host to donor tissue; (2) physiochemical aspects of donor and host cornea; (3) metabolic deficiencies of the host cornea. Fortunately, the corneal tissue has low antigenicity because of its avascularity and cellular paucity. However, hypersensitivity reactions do occur and may lead to vascularization, infiltration, and permanent clouding of the graft. The exact nature and cause or causes of these reactions in human corneal homografts remain to be elucidated. Race and sex are considered insignificant in the selection of donor material, and blood type incompatibility (ABO, Rh) does not alter the incidence of success.

Consideration of the donor cornea as a precise architectural framework upon which the regenerating host tissue is dependent would suggest that any divergence from structural normality in the donor cornea will unfavorably influence the final clarity of the graft. The presence of scar tissue, then, may impede the regenerative process by constituting a barrier to the migrating host cells, while the existence of adventitious blood vessels in the normally avascular cornea signifies a derangement of the physical and chemical factors underlying corneal transparency.

At least two elements seem to be involved in the resumption of normal metabolic activity after keratoplasty: (1) supply of metabolites by way of the limbal vessels, and (2) normal host cells. An intact vascular plexus in the limbus is essential if amino acids and other metabolites are to reach the regenerating cornea. In addition, the intracellular enzymes, on which the synthesis of protein and ground substance depends, will be deficient if the corneal cells of the host are either quantitatively or qualitatively abnormal.

Comments: The author reviews some of the more pertinent literature dealing with the causes of graft clouding, as well as the known facts and theories proposed as to maintenance of graft clarity.

His inference that proper case selection is still the greatest factor favoring a successful optical corneal graft is still probably true. This paper is a worthwhile contribution to the available literature dealing with corneal grafts.

ROBERT D. MULBERGER

RETINA

THE RELATIONSHIP BETWEEN EYE AND KIDNEY PATHOLOGY IN THE DIABETIC RAT

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A. M. A. Arch. Path., 1959, *67:* 386–394

Several investigators have shown that vascular lesions may occur in various parts of the body in uncontrolled or poorly controlled human diabetes; the chief disability is usually in the retina and kidney. Production of glomerular and retinal lesions in a diabetic animal would enable one to set up experiments in an attempt to modify these pathologic changes and perhaps give some clue as to their etiology.

Adult rats of the Long-Evans strain, which had been inbred for 30 years, were used in this study. After a 48-hour fast the animals were given subcutaneous injections of 115 to 125 mg. of alloxan per kilogram of body weight. Over 200 animals having blood sugar levels of at least 250 mg. per 100 ml. were used. The severity of diabetes was checked at least once a month by determining blood sugar levels or presence of glycosuria or both. Animals which did not maintain high blood sugar levels or a 4+ urine sugar were discarded.

These rats show a relationship between the pathologic changes of the eye and kidney. By the time cataracts are mature definite kidney glomerular lesions are present. Later, certain vessels may rupture into the anterior chamber of the eye, causing marked alterations in this organ. If the kidneys are examined in such animals, glomerular alterations are very severe. In fact, many renal corpuscles take on the appearance of Kimmelstiel-Wilson nephropathy. The lesions in both the eye and kidney can be attributed to abnormalities of blood vessels, the cause of which is not clearly understood. However, these changes are not strictly comparable to those found in the human diabetic. Retinopathy *per se* was rarely encountered in the diabetic rat. Examination of over 200 diabetic animals revealed a striate hemorrhage in only one animal, which had been diabetic for 8 weeks.

Comment: The pathogenesis of the vascular lesions underlying diabetic retinopathy, nephropathy and neuropathy remains obscure. It is important to find a counterpart to these lesions in experimental animals. In rats made diabetic with alloxan the author has noted nephropathy, cataracts and hyphemas, but no retinopathy.

Hyphemas and nephropathy in rats are reminiscent of the effects of choline deficiency. This may relate to the impaired liver function and vitamin deficiencies suspected in the diabetic animal.

Although several observers have described nephropathy in rats after alloxan or pan-

createctomy, others have failed to find such changes in diabetic animals. Some have reported equal incidences in diabetic and nondiabetic rats. Such differences in findings may result from the use of different strains of rats.

Unfortunately in the present report, no incidence rate is given for the nephropathy nor are studies reported of possible pathogenic factors. It would be of great interest to know what differences existed between the group of rats that developed nephropathy and the remaining diabetic rats that failed to do so. Such factors as diet, severity of diabetes, "control," acidosis, adrenocortical function, etc. would be of considerable interest. It is hoped that such studies will be the subject of forthcoming papers from this laboratory.

BERNARD BECKER

INVOLVEMENT OF THE EYES IN PERIARTERITIS NODOSA

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This is the case of a 64-year-old woman who died of intracerebral hemorrhage, after at least 3 years of cardiovascular hypertension. Retinal detachment together with a bizarre clinical course suggested the diagnosis of periarteritis nodosa, which was confirmed by autopsy. Histologic sections of both eyes showed marked hypertensive retinopathy with macular edema, papilledema, eosinophilic deposits in the retina, and retina detachment. A few areas of active nongranulomatous uveitis were found in both eyes without obvious involvement of the choroidal vessels. It is assumed that in this case the detachment was due solely to the hypertensive retinopathy. The authors believe this is the first case of an eye with retinal detachment in periarteritis nodosa that has come to a histologic examination.

Comment: Could the scattered foci of nongranulomatous infiltration around some of the uveal vessels in this most interesting case mask the beginning of the primary connective tissue injury of some of these vessels and be an inflammatory response to it?

Distribution, also by degree, of the characteristic collagen alterations is notoriously segmental in these diseases and one might encounter in some tissues an almost insignificant beginning. In that case, one might debate again the pathogenesis of the retinal detachment.

BERTHA A. KLIEN

RETINOPATHIES CONTRASTED

Diagnostic and Prognostic Significance of the Optic Fundi in Accelerated Hypertension

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Since many disorders which primarily or secondarily affect the vascular system may exhibit manifestations in the eyegrounds which appear superficially similar it is important for the physician to recognize and distinguish those retinal lesions which show characteristic features. Reflex color photography of the ocular fundus has several advantages over ophthalmoscopic examination. It does not require the full cooperation of the patient. Serial photographs on the same patient can document the natural history, variability and reversibility of retinal lesions and bring notice to subtle changes which might escape detection when the examiner has to rely on his recollection of previous examinations. When correlated with the clinical course of the disease they help to clarify both the diagnostic and prognostic importance of retinopathy.

The 114 color photographs which accompany this paper were taken during a 5-year study of retinopathy. They were made with a Bausch and Lomb retinal camera at a carbon arc intensity of 10 amperes and a shutter speed of $\frac{1}{15}$ of a second. Eastman daylight Kodachrome film was used. Two views of the fundus were taken routinely, one with the camera centered on the optic disk and the other midway between the disk and the macula. The photographs that illustrate this paper were chosen to demonstrate the following conditions:

1. The normal optic fundus.

2. Characteristic features of the retinopathies associated with: A. Advanced and accelerated hypertension. Hemorrhages seen in the advanced form are classically those of the nerve fiber layer type and may be of arterial, venous or capillary origin. In the accelerated form they are most commonly located within 2 or 3 disk diameters of the nerve head. Although they occur in greater profusion when papilledema coexists, swelling of the nerve head is not a prerequisite for their appearance. In some instances the proximity of hemorrhage to a nearby vessel may define the site of origin.

B. Diabetes mellitus. Capillary aneurysms lie in the inner nuclear layer of the retina, deep to the major vessels and nerve fibers. The hemorrhages which originate from them appear initially as rounded or oval extravasations with sharply demarcated edges. In advanced stages subhyaloid or vitreous hemorrhages may be observed. When the vitreous type undergoes organization rather

than resorption, the occurrence of new growth of delicate blood vessels and connective tissue may produce the picture of proliferating retinitis.

C. Leukemia and anemia. The retinopathy of leukemia and many anemias is characterized by white-centered hemorrhages in the nerve fiber layer. Leukemia tends to produce larger, more massive hemorrhages with large white centers. Their appearance can be correlated more consistently with fall in the hemoglobin level than with thrombocytopenia. Restoration of hemoglobin results in resorption of the hemorrhage. In anemias, when the hemoglobin level falls to 5 gm. or less, white-centered, oval or diamond-shaped hemorrhage may be observed in the fundi. In pernicious and nutritional megaloblastic anemia they may assume moderate size but usually they are smaller than those seen in leukemia.

D. Subhyaloid, or preretinal, hemorrhages appear shiny red and have smooth, rounded, sharply-defined borders. They vary in size from tiny, blister-like bulges to massive blebs obscuring a major portion of the fundus.

E. Retinal and preretinal hemorrhages associated with intracranial bleeding of the subdural and subarachnoid type vary in size and configuration. Since reflections of both the dura mater and the arachnoid membrane extend with the optic nerve within its sheath toward the posterior portion of the globe, potential channels are provided by which blood can dissect directly from a bleeding point in the central nervous system along the optic nerve.

F. In acute active forms of renal disease white fluffy conglomerates ("cotton wool patches") of edema frequently localize in the nerve fiber layer. They vary from a pinpoint to a disk diameter in size, are irregular in shape and usually show furred or striated margins. They are readily resorbable and usually disappear without residual in 3 to 4 weeks. Frequently, solitary white patches are situated at the bifurcation of retinal arteries; these are indistinguishable from the so-called cytoid bodies which may appear in association with collagen disease when renal involvement is severe. In contrast, discrete yellow and white punctate exudates frequently become widely distributed through the fundus in patients with *chronic renal disease*, especially in those with retinal vascular damage from hypertension. They lie deep to the major retinal vessels and disappear much more slowly than the cotton wool patches and thus most likely reflect a more severe degree of retinal ischemia. The macular star figure is considered by many as an ocular sign of renal disease.

3. Hypertension and papilledema. Papilledema is regarded as the most consistently reliable sign that hypertension has entered an accelerated phase. However, it may also be seen in conditions (acute glomerulonephritis, lead poisoning, etc.) in which hypertension may be merely an associated concomitant, and in complications (intracerebral or spontaneous subarachnoid hemorrhage, leaking berry aneurysm) which may befall the hypertensive patient. The success of management of the causative episode will be a better guide to prognosis in such instances than will the mere presence of papilledema.

When papilledema has subsided its previous presence and extent sometimes can be suspected when ophthalmoscopic examination reveals a grayish halo

surrounding the optic disk. This has been thought to represent a cuff of unresorbed edema fluid, but in some instances the gray ring may be noted for as long as a year after the disappearance of papilledema. If peripapillary exudates persist after subsidence of actual nerve head swelling, the postpapilledema halo is rather sharply set off from the surrounding fundus and the disk appears to float.

4. Retinopathy and blood pressure level. There has been no satisfactory demonstration that blood pressure height *per se* is responsible for the retinal changes that usually are seen in severe (grades 3 and 4) hypertensive retinopathy. Advanced retinopathy may sometimes be absent in patients with extremely high diastolic levels, and the converse is also true. Such instances emphasize the need for a clearer understanding of the natural history and reversibility of hypertensive retinopathy with respect to changes in blood pressure level.

A. Reversibility of retinopathy in pheochromocytoma. An unusual opportunity to observe the reversibility of retinopathy was afforded by a woman referred 2 months after termination of a pregnancy for presumed pre-eclampsia. She complained of headache, nervousness, weakness and sweating spells. The blood pressure ranged from 100/70 to 250/150 mm. Hg and she had pronounced postural hypotension and clinical evidence of hypermetabolism. When first seen her left fundus showed marked papilledema, occasional hemorrhages and numerous soft cotton wool patches. Although her blood pressure level was reasonably well controlled with antiadrenergic drugs, for 2 months before surgical removal of a pheochromocytoma, the retinopathy worsened and visual acuity was moderately affected. Four weeks after the operation and restoration of blood pressure to normal, papilledema was still present and heavy macular exudates had been laid down. Many of the smaller vessels had been completely obscured. Photographs taken 10 weeks to 10 months after surgery show progressive dissipation of the exudates with prolonged persistence of the postpapilledema halo.

B. Reversibility of retinopathy in chronic glomerulonephritis. Even after moderate renal insufficiency develops in chronic glomerulonephritis the further course may be protracted. Here observation of serial retinal changes with relation to other clinical and laboratory manifestations often yields correlations which emphasize that factors other than blood pressure level are important in the production of neuroretinopathy. One patient was followed over 3 separate bouts of retinopathy (papilledema and macular exudate) coinciding with congestive heart failure although the blood pressure remained unchanged.

C. Hypertensive encephalopathy with retinopathy. Grade 3 or 4 retinopathy is an almost constant companion to the headache, vomiting, convulsions, coma and rise in blood pressure which characterize the syndrome clinically. Since certain of these manifestations are rapidly transient, the fate of the associated retinal changes assumes added importance in clinical follow-up. The cases illustrated include two in which the retinopathy, with migration of edema residues toward the macula, persisted even in the presence of uremia, and five in which the retinopathy improved although hypertension persisted. The retinal

improvement may be entirely independent of the clinical course of the disease. That accurate retinal evaluation can sometimes contribute to differential diagnosis is shown by the case of a woman admitted with a diagnosis of hypertensive encephalopathy presenting with severe headache, nausea and vomiting. Both fundi showed papilledema but the single hemorrhage present was dark-centered and surrounded by a red halo, resembling the subhyaloid retinal hemorrhages seen with subarachnoid bleeding. Spinal fluid findings and subsequent clinical developments confirmed subarachnoid hemorrhage as the correct diagnosis.

5. Disappearance of small caliber retinal vessels concomitant with progression or renal disease. It has been suggested that the slower resorption of exudates ("albuminuris retinitis" and the macular star figure) in patients with chronic renal impairment reflects a functional inadequacy of the retinal vessels, possibly the result of hypertensive damage. This concept is supported photographically by six examples illustrating the apparent disappearance of small caliber retinal vessels (both arterial and venous) in patients with prolonged renal insufficiency.

6. Progression and regression of hypertensive retinopathy with and without lowering of blood pressure level by antihypertensive agents. The examples presented here again emphasize that the first appearance of advanced retinopathy correlates reasonably well with other clinical evidence that hypertension has entered an accelerated phase, but the clearing of such retinal changes could not be correlated consistently either with blood pressure level or with the further course of the disease.

Comment: This is an elementary account of the retinopathies and neuroretinopathies accompanying the most common systemic diseases, illustrated by beautiful serial fundus photographs, emphasizing the sequence of progression or regression.

Oversimplification is probably an inherent danger in such reviews, resulting for instance in the statement that lack of absorption of a vitreous hemorrhage is the cause of proliferating retinitis in advanced diabetes.

Concerning the pathogenesis of retinal and subhyaloid hemorrhages occurring in subdural or subarachnoidal bleeding there is almost general agreement now that they do not arise from direct continuity of the intracranial hemorrhage along the optic sheaths but that they are due to bursting of small veins from sudden increase of venous pressure in the intracranial cavity, the orbit, and the retina, each vascular bed producing hemorrhage independently from the other.

Regarding the reversibility or lack of it of some of the hypertensive changes, it should be emphasized that the presence or absence of organic vascular lesions is the deciding factor.

BERTHA A. KLIEN

NEURO-OPHTHALMOLOGY

THE PSYCHIATRIC COMPLICATIONS OF TOXOPLASMOSIS

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Lancet, 1959, *1:* 1180–1182

Beattie (Tr. Roy. Soc. Trop. Med. & Hyg., *51:* 96, 1957) found that in Lincolnshire 36 per cent of country dwellers and 22 per cent of town dwellers had cytoplasm-modifying antibodies which gave positive results for toxoplasmosis with the dye-test technique described by Sabin and Feldman, 1948.

Two types of infection have been described:

1. A congenital form, characterized by encephalomyelitis, cerebral calcification, hydrocephalus, and chorioretinitis, with symptoms apparent either at birth or soon after. The prognosis is very poor, and those patients who survive are usually mentally retarded and epileptic.

2. An acquired form, which falls into four clinical groups—cerebrospinal, exanthematous, glandular, ophthalmic.

It has been suggested that in the adult chorioretinitis may be the only sign of infection; according to fairly recent estimates 20 to 35 per cent of cases of chorioretinitis are caused by toxoplasmosis. Although there is evidence of nervous-tissue involvement by *Toxoplasma gondii*, few references to psychiatric disorder associated with this condition have been found. The authors describe a case of congenital toxoplasmosis with an exacerbation in adult life presenting as an acute psychotic illness.

A young woman, aged 22, was hospitalized with an acute schizophrenic-like syndrome. At first admission, in September 1957, she had a blank unemotional expression and her responses were slow. Her psychiatric state was thought to be early catatonic schizophrenia. On readmission 4 months later, she was elated and overactive, despite threats of suicide. She discharged herself against advice after 3 weeks. Two months later she was admitted again because she was noisy and difficult at home.

On physical examination both optic fundi showed areas of longstanding chorioretinitis, with numerous scattered minute lesions. All lesions were probably congenital; in the right eye there was a large lesion about the size of the optic disk. The maculae were normal. Toxoplasmosis tests showed a titer of 1/16, and the complement-fixation test was negative. These findings were "consistent with but not diagnostic of toxoplasmosis."

The two possible diagnoses in this case were: (1) behavior disorder associated with toxoplasmic infection, and (2) catatonic schizophrenia. The presence of chorioretinitis, with a history of meningitis in childhood and convulsions until age of 5, suggested a toxoplasmic infection. Although the result of the dye

test was not reinforced by the results of other tests, the reason for this may have been that the investigations were made a year after the acute illness.

A dye-test titer of 1/16 is compatible with a longstanding toxoplasmic infection but not diagnostic of it. In the present case there were three other features—chorioretinitis, a history of fits with abnormal E.E.G. findings, and mental retardation. In addition, during a pyrexial illness in 1957, she had an urticarial rash. It has been noted that the adult infection can present in an exanthematous form. The symptoms of schizophrenia which were apparent in 1957 have completely resolved, and it would be difficult to sustain that diagnosis.

Comment: It is important for ophthalmologists to be aware of the possibility of psychiatric complications associated with toxoplasmosis. He may be the consultant who will see the chorioretinitis and be able to suggest the diagnosis of toxoplasmosis. He thus is in a position to be helpful to his colleagues in patients who may have psychiatric problems. His awareness of the possibility is one step toward the proper diagnosis.

IRVING H. LEOPOLD

PSYCHOGENIC VISUAL DISTURBANCES

JEROME M. SCHNECK

Department of Psychiatry, State University of New York College of Medicine, New York, New York

New York J. Med., 1959, *59:* 2031–2032

Three examples of psychogenic visual disturbances encountered in psychiatric practice are described because of their pertinence for the general physician and ophthalmologist as well as the psychiatrist. It was possible to correlate the visual problems with the other aspects of personality functioning so that more complete views of the personality disturbances were available. Specific symptoms were persistence of a film or veil over the field of vision, intermittent blurring, and amblyopia.

In one of the cases, that of a 34-year-old man, under treatment for an anxiety reaction, psychiatric study revealed that blurring occurred only when the patient focussed on certain objects. They might be buildings, city landmarks, or other familiar items. Further study showed that this occasional selective blurring in its distortions was a psychologic representation of his striving with difficulty to see himself in new perspectives. As personality changes occurred, the blurring episodes diminished.

The first two patients displayed symptoms reflecting partial withdrawal. The third patient exhibited extensive retreat through major symptomatology. Her emotional turmoil was reflected in the change from overt aggression and hostility

to hostility disguised as helpless dependency. The psychogenic amblyopia was a poor compromise. These correlations are of concern to all physicians in contact with such problems, since they can point toward steps leading to successful adaptation, growth, and general well being.

NEURON DOCTRINE AND ELECTROPHYSIOLOGY

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The Department of Zoology, University of California, Los Angeles, California

Science, 1959, *129:* 997–1002

The neuron doctrine, which is chiefly due to Cajal, was unquestionably a giant stride forward in the understanding of the substratum of nervous function. It forms the basis of all modern work on the nervous system. It asserts that the nerve cell and its processes, together called the neuron, form the cellular units of the nervous system which are directly involved in nervous function; that all nerve fibers are neuronal processes; that the neuron and all its extensions develop embryologically from a single neuroblast; and that the neuron is a trophic unit, all its processes being dependent upon the nucleated cell body for their maintenance and regeneration.

As a subsidiary doctrine, Cajal made the brilliant inference from the anatomic arrangement of sensory, motor, and internuncial neurons that they are all dynamically polarized, usually in such a way that excitation can only be transmitted from the axon of one neuron to dendrites or soma of the next and, within a neuron, must normally spread from dendritic to axonal poles.

Although this is not inherent in the original anatomic concept, the neuron has classically come to be regarded as a functional unit, and it is here that newer information forces a reappraisal.

The strides made in electrophysiology from the time of Helmholz in the middle of the last century to the period just before and after World War I led to the discovery of the change in electrical potential with action which, in the single nerve fiber, came to be called the nerve impulse. This was found to be an all-or-none event of the order of 1 millisecond in duration and capable of following a preceding impulse only after a short interval. Thus, the concept of a quantum of activity or a unit of function came to be emphasized, and the nervous system came to be regarded as a kind of digital computer with a binary—that is, yes-or-no—response. Some would prefer to call it a pulse-coded device, since the intervals between pulses are graded and can introduce noise.

The four basic tenets that grew out of the impact of electrophysiology on the neuron doctrine during the period of the 20's and the 30's still dominate much of the thinking in the field. These are (1) that the all-or-none impulse is synonymous with the neuron in action; (2) that when any part of the neuron is excited, this excitation spreads to all parts of the neuron as a propagated nerve impulse;

(3) that Cajal's doctrine of the dynamic polarity of neurons meant that dendrites propagate impulses towards the cell body; and (4) that the secret of all labile functions must lie in the properties of a junction between neurons. This locus, called the synapse, was supposed to be the only seat of selection, evaluation, fatigue, and facilitation, and perhaps of long-persistent changes as well.

The evidence of the last few years has significantly altered all four of these tenets. Although, anatomically, the neuron doctrine has never been more firm, physiologically, there is a new appreciation of the complexity-within-unity of the neuron. Like a person, it is truly a functional unit, but it is composed of parts of very different function not only with respect to metabolism and maintenance but also in the realms of processing diverse input and determining output—that is, of integration. The impulse is not the only form of nerve cell activity; excitation of one part of the neuron does not necessarily involve the whole neuron; many dendrites may not propagate impulses at all; and the synapse is not the only locus of selection, evaluation, fatigue, and persistent change. Several forms of graded activity—for example, pacemaker, synaptic, and local potentials—each confined to a circumscribed region or repeating regions of the neuron, can separately or sequentially integrate arriving events, with the history and milieu, to determine output in the restricted region where spikes are initiated. The size, number, and distribution over the neuron of these functionally differentiated regions and the labile coupling functions between the successive processes that eventually determine what information is transferred to the next neuron provide an enormous range of possible complexity within this single cellular unit.

In the face of this gradual but sweeping change in functional concepts, any statement but the most diffuse about expectations for the future must be dangerous. Nevertheless, the suggestion may be hazarded that in the near future new insight may be gained at this unitary level of neurophysiology with respect to the functions of and differentiations among dendrites, the chemical and perhaps ultramicroscopic specification of different kinds of surface membrane, additional labile processes, sites of possible persistent change, and the normal functional significance of intercellular reactions mediated by graded activity without the intervention of all-or-none impulses.

THE ENCEPHALOGRAM IN INTERNAL CAROTID ARTERY OCCLUSION

FLETCHER MCDOWELL, CHARLES E. WELLS AND CAROL EHLERS

Neurology, 1959, *9:* 678–681

This study reports of encephalograms which have been performed on 20 patients admitted to the Second Neurological Service of Bellevue Hospital or to the neurology service of the New York Hospital, New York City—having throm-

bosis of the internal carotid artery confirmed in each instance by carotid arteriography.

In 18 patients unilateral occlusion was demonstrated in one bilateral occlusion; in one incomplete occlusion. There were 15 male and 5 female patients the ages varied from 37 to 72 years. A total of 36 electroencephalograms was made on the 20 patients, at periods varying from 4 days to 6 years after the onset of clinical symptoms.

In all of these 20 patients the electroencephalograms were considered to be normal. The most prominent electroencephalographic abnormalities were the presence of diffuse low amplitude slow wave activity in 19 patients, usually confined to the side of the lesion but at times appearing bilaterally—and focal higher amplitude slow wave activity in 19, on the side of the insufficiency in 16.

The severity of the electroencephalographic changes appeared to bear little relation to the severity of the clinical symptoms. In patients followed serially there was usually slow improvement, though the electroencephalogram often remained markedly abnormal for many weeks or months.

These electroencephalographic abnormalities, while quite consistent within the group studied, are probably not specific for internal carotid occlusion, since they might also be expected to appear in other varieties of occlusive vascular disease. They frequently resemble the patterns seen in cerebral neoplasm. The most important differential point according to this study is that the record tends to improve with time in internal carotid occlusion, whereas this is not usually the case in cerebral neoplasm.

Although the electroencephalographic changes are not specific for internal carotid occlusion it was felt that when the electroencephalographic findings are combined with clinical evaluation and adjuvant methods of examination the diagnosis of internal carotid artery occlusion could be made without resort to arteriography.

Comment: Although the clinical evaluation, ophthalmodynamometry, auscultation of the cranium for bruits, observations of the conjunctival vessels and pharyngeal palpation for the internal carotid pulse and especially arteriography—the latter regarded as the diagnostic method of choice—have been advocated to aid the clinician in the diagnosis of internal carotid occlusion, this report calls attention to the encephalogram as further diagnostic aid.

RUTH FABRITIUS

CLINICAL AND ELECTROENCEPHALOGRAPHIC CONSIDERATIONS IN THE DIAGNOSIS OF CAROTID ARTERY OCCLUSION

WILLIAM K. HASS AND ELI S. GOLDENSOHN

Neurology, 1959, *9:* 575–589

This study deals with a series of 35 verified cases of partial and complete carotid artery occlusion emphasizing the nature, extent, and duration of electroencephalographic abnormalities and their relationship to the clinical picture. These patients were treated at the Neurological Institute of New York between 1949 and 1957 and their studies included at least one electroencephalogram and verification of the diagnosis by arteriography (31 patients), post-mortem examination (2 patients), angiocardiography (1 patient), and operation (1 patient). The examination consisted of monopolar and bipolar recordings from 18 scalp areas. Each electroencephalographic study had been dated from the time of the most recent exacerbation of symptoms rather than from the time of onset of the initial symptoms.

Of the 35 patients 26 were men and 9 women; ages ranged from 40 to 73 years, the average age being 56. The left internal carotid artery was the site of the lesion in 20 patients, the right in 11. In 2 patients, who subsequently died, severe bilateral internal carotid lesions occurred. The two remaining cases showed atherosclerotic occlusion in the cervical portion and in the intracranial portions of both carotid arteries respectively.

Normal electroencephalograms were exhibited in 9 patients either initially or at some point in the course of the disease. Abnormal electroencephalograms occurred in 29 patients some time during their illness; although a tendency existed in some patients for the tracing to revert toward electrical normality, persistent marked abnormalities were noted for periods of 2 weeks to 18 months in 15 patients.

According to these studies the electroencephalogram in carotid occlusive disease may not only persist but become progressively worse with time, simulating serial records seen in patients with brain tumors. In order to compare the degree of neurologic deficit with the electroencephalographic changes, the severity of neurologic impairment was graded at the time of each electroencephalogram. This grading revealed a general tendency for the degree of electroencephalographic abnormality to parallel the severity of the symptoms.

The study could demonstrate a number of valuable clinical diagnostic features in patients with unilateral carotid disease such as marked preponderance in men, onset largely in the fourth or sixth decades, marked tendency for the contralateral upper extremity to be the site of the initial motor or sensory symptoms, infrequent involvement of the optic radiations, infrequent complaint of headache, infrequent appearance of seizures, infrequent high blood pressure, persistence of palpable carotid pulses in almost all patients and normal cerebrospinal fluid and erythrocyte sedimentation rate values as a rule.

The electroencephalographic studies were less specific, they were mainly of the focal slow-wave variety, such as is often encountered in brain tumor. The frequency of changes was 83 per cent, not significantly different from that of brain tumor.

Comment: The difficulties of comparing groups of patients with internal carotid disease admitted to the hospital with more persistent and severe neurologic deficits have been pointed out by these investigators. Selection occurs before the patient enters the hospital thereby weeding out patients with mild and transient symptoms. The degree of electroencephalographic abnormality generally paralled the severity of neurologic deficit.

A number of valuable clinical diagnostic features could be demonstrated in this group besides the fact that the encephalographic changes did not reveal any single electrical abnormality which would be specific for cerebral dysfunction secondary to carotid occlusive disease. Furthermore the severe changes observed—most similar to those seen in intracerebral space occupying lesions—persisted from months to more than a year contrary to the commonly accepted notion of rapid resolution of electroencephalographic abnormalities with time.

RUTH FABRITIUS

Pediatric Ophthalmology

OPHTHALMOLOGICAL SUSPICION OF UNRECOGNIZED CONGENITAL TOXOPLASMOSIS

EDITORIAL

Clin. Proc. Child. Hosp., 1959, *15:* 125

Toxoplasma gondii are protozoa which reproduce only within a host cell. Proliferation of the organisms is followed by cell destruction and parasitemia. Focal cellular necrosis and inflammatory reaction ensue in various tissues under attack, such as heart, lung, liver, spleen, lymph nodes, brain, retinas and skin. Neutralizing antibodies appear during the first one to three weeks of the disease, and with development of immunity the parasitemia subsides while repair of the cellular necrosis proceeds in the extraneural viscera. As the parasites retreat from their piracy tactics of cellular invasion and destruction they accumulate in large numbers within the membrane of a captured cell, thereby deceptively avoiding antibody detection since the pseudo-cyst elicits no chemotactic response. In this state they survive for the lifetime of the host unless the pseudo-cyst happens to rupture. At some indefinite date after onset of the disease the majority of chronically infected hosts develop an allergy to the products of the parasite. This is manifest by a skin hypersensitivity to toxoplasmin similar to the tuberculin reaction.

Embryonic and fetal neural tissue (brain and retinas) are especially susceptible to severe involvement by these protozoa which are transmitted to the fetus via the placental circulation while the infected mother almost never demonstrates clinical evidence of a neural tissue lesion. If the fetus survives, healed stigmata of the irreparable damage to neural tissue are often apparent. Recognition at birth of the active disease or of these healed neural tissue stigmata, supported by positive serological antibody titers in both infant and mother, allows the presumptive diagnosis of congenital toxoplasmosis. However, the prenatal illness may resemble the usual symptomless acquired adult illness. This raises the question: How often do the mother and fetus share the same unrecognized toxoplasma infection?

A new concept of chorioretinitis in older children and adults reflects the importance of this question. Heretofore, an initial episode of chorioretinitis occurring in an older child or adult associated with positive serological evidence of toxoplasmosis had been attributed to a newly acquired infection. More recently this concept is criticized for the following reasons: (1) Retinal invasion

is very rare in acquired toxoplasmosis; (2) although chorioretinitis may not be present at birth in a congenital toxoplasmic infant, it may appear at some later date (a recent study showed only 40 per cent of 75 congenital toxoplasmic infants had chorioretinitis at birth which increased to 80 per cent when the surviving infants were later examined); and (3) congenital toxoplasmosis probably is often unrecognized.

The new hypothesis is that late ocular toxoplasmosis usually represents an allergic inflammatory response to a ruptured pseudo-cyst which has persisted in the retina from a prenatal infection that was not recognized as congenital toxoplasmosis. The histological picture is in keeping with this hypothesis, and differs in many respects from the predominantly acute necrotic chorioretinitis with abundant intracellular toxoplasma seen in the eyes of fatal congenital cases. It is reasoned that the toxoplasma liberated from the pseudo-cyst remain scattered without being able to invade and multiply within new cells, and are destroyed by antibodies, their products being the allergens which incite the allergic response in the surrounding hypersensitive tissue. This hypothesis is somewhat supported by the fact that so many cases of adult chorioretinitis attributable to toxoplasmosis rapidly reach a peak of inflammation within days and gradually subside over a period of four to six weeks.

MARSHALL M. PARKS

CHLORAMPHENICOL DOSAGE IN THE NEWBORN INFANT. THE "GRAY SYNDROME"

EDITORIAL

LEONARD APT

The Wills Eye Hospital, Philadelphia, Pennsylvania

Many pediatricians consider chloramphenicol the drug of choice for the initial treatment of infections in infants and children. There are valid reasons for this preference. Chloramphenicol has a broad spectrum of antibacterial activity. The majority of strains of staphylococci are still susceptible to the drug. Chloramphenicol is highly effective against many Gram-negative bacteria, bacteria which as a group are one of the principal causes of neonatal sepsis. Ophthalmologists also prefer chloramphenicol for the initial therapy of intraocular infections for these reasons and in addition because of its superior penetration into the ocular tissues.

Recently chloramphenicol has been found to be toxic in doses previously recommended for the newborn infant. A few deaths have occurred in premature infants coincident with the administration of the drug.

Chloramphenicol (also other drugs including the sulfonamides, barbiturates,

and morphine) is detoxified, for the most part, in the liver, and to a lesser extent in the kidney and intestine by the coupling of the drug with glucuronic acid. The glucuronides thus formed are filtered as well as secreted by the kidney. Free chloramphenicol is excreted only by renal filtration. The glucuronide detoxification mechanism and renal function may be incompletely developed in the newborn infant, particularly the premature infants. Thus a high, sustained, toxic blood level could be reached.

Chloramphenicol has been used in experimental work to inhibit protein synthesis. Toxicity in the newborn may be explained, at least in part, also by this action.

The clinical manifestations of chloramphenicol toxicity in the newborn are: abdominal distention with or without vomiting and diarrhea, hypothermia, cold clammy skin, progressive pallid cyanosis (gray—thus the name "gray syndrome"), hypotension, irregular respirations, and death. The signs appear within 2 to 3 days after the start of chloramphenicol therapy, but death may occur in as short a time as 18 hours.

The dosage of chloramphenicol ordinarily recommended for infants and children for the treatment of serious infections is 50 to 100 mg. per kg. body weight per day with a priming dose of 50 to 75 mg. per kg. body weight. In newborn infants (up to 1 month of age) the dosage should be reduced. It is suggested that the dosage during the early phase of treatment when response to the drug is closely observed should not exceed 25 mg. per kg. body weight per day in premature infants and 50 mg. per kg. of body weight per day in full-term infants. The priming dose should not be given.

Chloramphenicol is an extremely useful, effective, but potent drug. It must be given to newborn and young infants with extreme caution no matter what rule of thumb for dosage is used.

PRESCHOOL VISION SCREENING

FLORENCE CUNNINGHAM

Am. J. Pub. Health, 1959, *49:* 762–765

In 1925 the National Society for the Prevention of Blindness, working with 12 ophthalmologists, showed that preschool screening of children's eyes was both necessary and possible. Despite great progress in medical and health care of these younger children since this time, the detection and treatment of eye defects has been relatively neglected.

According to Moran, the most important reasons for preschool eye tests are discovery of refractive errors and of suppression amblyopia. Treatment of amblyopia due to strabismus after the school age rarely restores normal vision,

but much can be done if the condition is recognized early. The time and money expended in rehabilitating a preschool child with a life expectancy of 60 to 70 years is surely as worthy as the restoration of vision in adult with a life expectancy of 10 to 20 years. Moreover, study of children who require special help in school because of partial vision shows that most of them have congenital trouble, so that they should have received special education from the beginning.

Since 1951, the National Society for the Prevention of Blindness, working with local health departments, has conducted 34 continuing preschool vision-testing projects, using volunteers. Altogether 55,179 children have been screened, of whom 2,286 were referred for eye care. Although the percentage of referrals varies considerably in different communities, it averages between 5 and 6 per cent of the total number. Of examples cited in this paper, between 73 and 100 per cent of referrals have needed eye care. Moran's analysis of the Louisville study showed: refractive errors in 50 per cent, oculomotor anomalies in 20 per cent, congenital defects in 3.5 per cent, external diseases in 4.5 per cent, and low refractive errors to be kept under observation in 10 per cent.

If a community is interested in undertaking a preschool eye-service project of this type, the field-service director of the National Society for the Prevention of Blindness gets in touch with local ophthalmologists and health departments, who then usually develop a basic plan to be discussed with the local medical society. A committee is then set up, including ophthalmologists and members of the health department, to determine the details of the project. Screening is most commonly carried out in the nursery school, but various other sites are used in some communities. Volunteers for carrying out the tests and public education are drawn from various local organizations.

The Snellen "E" chart is used in all tests, and results are as far as possible correlated with observations by the volunteers and nursery school teachers. Usually 3-year-olds are referred for visual acuity of 20/50 or less, and 4- to 5-year-olds for visual acuity of 20/40 or less. Some also refer children for differences in acuity between the two eyes. Children who do not see the critical line are screened a second time. Some centers add other tests. Teams of three volunteers do the actual tests, with either an additional member, or in public health projects a public health nurse, to interpret records. Experience indicates that visual acuity can be checked in 60 per cent of children 3 to 3½ years old, in 74 per cent of those 3½ to 4, and in 96 per cent of 4-year-old children.

Comment: Preschool vision screening, I am happy to learn, was, after all, initiated by ophthalmologists of New York City. A regular reader, like myself, of the nonmedical eye-care literature easily gets the notion that ophthalmologists never heard and never cared about vision screening in children. This report by Miss Cunningham, a registered nurse, is certainly reassuring. Preschool vision screening, carried out by lay volunteers, without expensive equipment, found between 5 and 6 per cent of the children in need of further study, and the referrals were justified, in general, in as much as 85 per cent. In fact, in one community, Schenectady, New York, where out of 914 children, 36 were referred for further study, "every child referred but one has had an eye examination, and *there have been no incorrect referrals*" (italics by me). Public health officials should rush

to consult Miss Eunice Haushalter, public health nurse of the Schenectady County Public Health Committee. She must hold the secret to proper screening and effective persuasion.

It is interesting to learn that the standard recommended by the National Society for the Prevention of Blindness (this wonderful organization whose efforts stand behind all these results) is 20/50 for the 3-year-old child and 20/40 for the 4- and 5-year-old and that unequal vision is looked upon as a cause for referral even if vision is within passing standards. With all this, I heartily agree. I wonder, however, if the cover test is one volunteers can really use to any advantage. It takes the fledgling ophthalmologist a long time to learn how to evaluate it.

ARTHUR LINKSZ

USE OF CONTACT LENSES BY A THREE YEAR OLD PARTIAL ALBINOTIC WITH HIGH MYOPIA: CASE REPORT

J. MYRON MIDDLETON

Beverly Hills, California

Eye, Ear, Nose & Throat Month., 1959, *38:* 565–568

According to Duke-Elder, the incidence of albinism is 1 in 10,000. This would indicate that there are about 17,000 albinotics in the United States. No references, however, have been found in the literature reporting the wearing of corneal contact lenses by a child in the 3-year-old age group. Consequently, the presentation of this case appears timely.

The vision of the author's patient, a 3-year-old boy with high myopia, subnormal vision uncorrectible by spectacles, partial albinism, periodic nystagmus, and heterophoria or tropia or both, was improved to a useful degree by carefully prescribed corneal contact lenses. About 45 office fittings, requiring some 100 hours of the examiner's time, had been carried out up to the time of writing, and the results so far secured show that the use of contact lenses is at least feasible in children of this age.

There is reason to believe that, physiologically, the more the light is allowed to enter the albinotic eye, the greater the stimulation of pigment formation. Moreover, if albinotic patients are to obtain visual benefits from contact lenses, they should be fitted at the age of 3 years at the latest to foster macular development. Methods of approaching these young children and securing their cooperation are outlined in the patient's case report, which is presented in detail.

Comment: One can only voice admiration for Dr. Middleton who spent about 45 fitting visits requiring some 100 hours of his time to provide contact lens correction for a 3-year-old child. We hope he succeeds and also hope that from time to time he will report on the progress of this case; and that his heroic "first" will stir others to similar firsts.

I think the effort is praiseworthy although eyeglasses, regular eyeglasses, might do just as well. The author thinks that "there is reason to feel that . . . the more light we allow to enter the albinotic eye the greater the stimulation for pigment formation."

I wish he were right. Dr. Kestenbaum lets albinotic babies look through pinholes to prevent stray light from entering through the sclera. Dr. Middleton wants to get more light into the eye. Kestenbaum hopes with his method to stimulate the formation of a macula immediately after birth. Middleton believes that his method will "foster macular development" even at the age of 3 years. Kestenbaum thinks that by the end of the first half year of life the chances to foster this development are over.

Certainly more research in this particular field is necessary. Also more activity. The efforts of both Kestenbaum and Middleton prove that standing-by might not be the wisest policy. Even if the theoretical basis is shaky, we must be thankful to all who at least try.

ARTHUR LINKSZ

THE INCIDENCE OF OPHTHALMIA NEONATORUM WITHOUT PROPHYLAXIS

EDWARD SOLOMONS, BENJAMIN KRAMER, WILLIAM W. STEIN AND SCHUYLER G. KOHL

Am. J. Obst. &. Gynec., 1959, *78:* 513

The use of silver nitrate eye drops as prophylaxis in the newborn reduced the incidence of ophthalmia neonatorum in Leipzig in 1880 from 7.8 to 0.49 per cent. In New York, the introduction of sulfonamides and antibiotics reduced the incidence of gonorrhea from 22,746 cases in 1947 to 11,479 in 1957, and the incidence of gonorrheal ophthalmia from 23 cases in 1945 and 1956 to between none and 8 cases yearly through 1956. Of 12 cases reported in 1957, 6 had prophylaxis and 4 came from the same hospital. Moreover, reports have appeared showing decrease even when no prophylactic treatment was used, or when sterile water only was dropped in the eyes.

In view of these observations, we compared the results of previous studies of 1,000 consecutive newborn infants receiving silver nitrate as prophylaxis and of 1,700 receiving tetracycline ointment, with two new series, totalling 5,480 infants, receiving either no treatment or only distilled sterile water. The presence or absence of edema was noted in all cases, and conjunctivitis was diagnosed on the basis of watery or purulent discharge, the latter classified from none to +1, +2, +3, and +4. The last two classes included moderate or severe purulent discharge.

The incidence of conjunctivitis did not differ significantly in treated and untreated babies, occurring in 16.8 per cent of those receiving distilled water and

in 17.5 per cent of those who had no treatment. The classification of discharge was also similar in the two groups, slight watery discharge predominating in all cases.

Cultures taken in 208 of the 951 cases of conjunctivitis disclosed organisms in 56 of 76 cases with purulent discharge and in 126 of 243 cases of heavy watery discharge, or in a total of 54.8 per cent of the entire series with conjunctivitis. The percentage of organisms did not vary significantly with treated and untreated cases. However, cultures were negative in 48.5 per cent of those with watery and in 35 per cent of those with purulent discharge. Staphylococci were cultured in 72 per cent of positive cultures, but *Staphylococcus aureus* in only 17.4 per cent. One suspected case of gonococcus proved negative.

Purulent discharge was found in 1.4 per cent of the present series, and in 17.5 per cent of the earlier series receiving silver nitrate prophylaxis and in 5.7 per cent of those given tetracycline ointment. The question arises as to the possible influence of chemical conjunctivitis in these earlier cases. Although differences in procedure make accurate bacterial comparison impossible, it seems likely that conjunctivitis with negative cultures may be due to virus infection or maternal irritants.

Because gonococcal conjunctivitis is rare and easily treated, and because of the danger of chemical conjunctivitis, the advisability of routine prophylactic treatment should be reconsidered and cultures made in incipient cases.

Comment: Another report has been added to others in which the modern incidence of gonorrheal ophthalmia in unprotected infants has been lower than the rate obtained by Crede with silver nitrate prophylaxis. The authors question the advisability of routine instillation of silver nitrate or antibiotics into the eyes of the newborn but they make no specific recommendations.

They are apparently unaware that an important cause of purulent discharge in the newborn, inclusion blennorrhea, can be readily diagnosed by microscopic examination of conjunctival scrapings taken with the platinum spatula of Halberstaedter and von Prowazek (1907) and stained by Wright's or Giemsa's method. One wonders how many of the 20 cases with purulent discharge but with negative cultures were caused by this agent. However, this consideration is partly academic in view of the fact that inclusion blennorrhea is not prevented by instillation of silver nitrate.

Neither, it would seem, is gonorrheal ophthalmia, at least in every case, since of 12 cases occurring in New York City in 1957, 6 had received prophylaxis, 5 of these with silver nitrate. But since routine silver nitrate prophylaxis, being required by law, was presumably given to all but a few newborn babies, these figures could also mean that the rate among unprotected infants was many times higher than the rate among those receiving prophylaxis.

The basic question to be answered is whether silver nitrate prophylaxis does more harm than good. Notwithstanding several surveys of several thousand unprotected patients, the fact remains that no one knows exactly what the incidence of gonorrheal ophthalmia would be if all prophylaxis were to be discontinued throughout the United States. Which would be more distasteful, a million cases of chemical conjunctivitis with negligible risk of blindness, or a thousand cases (0.1 per cent) of gonorrheal ophthalmia requiring treatment and carrying a certain risk of blindness if treatment were not started

in time? If these are the alternatives, your reviewer finds himself in favor of chemical conjunctivitis. But what if the expected rate of gonorrheal ophthalmia is only 50 to 100 cases per million births? What is the expected rate of failure to treat such cases until it is too late to prevent blindness? Here one must balance the remote possibility of permanent chemical injury against the remote possibility of untreated bacterial disease.

The principal value of studies such as the present one is in establishing the expected incidence of gonorrheal ophthalmia in unprotected infants. The findings reported by the Brooklyn workers and others justify experimental omission of routine prophylaxis on a large scale among infants under daily medical observation during the neonatal period. It would be of incidental interest to establish the frequency of inclusion blennorrhea at the same time.

HENRY F. ALLEN

EYE DISTURBANCES IN INFANCY AND CHILDHOOD

JOSHUA ZUCKERMAN

New York, N. Y.

Arch. Pediat., 1959, *76:* 211–236

The pediatrician should be acquainted with eye disturbances in children for he is generally the first consulted when parents suspect an abnormality. He may be the first to notice birth trauma, developmental defects, and ophthalmia neonatorum, which account for most cases of blindness in the newborn. Occasionally the pediatrician is faced with an eye disease that develops during the course of a general disease that he is treating.

The ophthalmic history in children is not complete unless details of the antenatal course, the delivery, the postnatal period and family diseases are obtained.

On examining a child's eyes close inspection with instruments should be left for the latter part of the examination to avoid frightening the patient. Casual observations from a distance of the patient's demeanor, gait, size and shape of the head, the position of the head, the appearance and movement of the eyes may detect congenital or acquired eye defects.

A general review of the congenital and acquired eye conditions is given in brief. The pediatrician should recognize these disturbances not only for their local significance but also interpret them in terms of systemic diseases.

Information is presented on the differential diagnosis between conjunctivitis and dacryocystitis, between true ptosis and pseudoptosis, between hordeolum and chalazion, between conjunctival and ciliary congestion, and between strabismus and pseudostrabismus.

The pediatrician can take care of simple lacerations of the eyelids, corneal abrasions, and foreign bodies of the cornea and conjunctiva, but he should refer

more serious injuries and chemical burns to the ophthalmologist. The danger of Pseudomonas contamination in fluorescein solutions is cited.

Functions of the eyes and their adnexa such as the ability to open or close the eyelids, pupillary reactions, vision, refraction, strabismus, motility, orthophoria and heterophoria are discussed for the pediatrician in simple terms.

Comment: Dr. Zuckerman has given a comprehensive review of the eye disturbances that may occur in a child. This is a difficult task for an author to accomplish in an article of ordinary length. Indeed at times it must be frustrating to any author of this type of article who realizes that completeness often will mean the mere listing of diseases or abbreviated descriptions. Moreover it must be taxing to the pediatrician reader who because of his limited knowledge and training in ophthalmology becomes overwhelmed with the specialized terminology, the scant accounts of ophthalmic diseases and their pathophysiology, and even with the names of the pieces of equipment that the ophthalmologist uses. Perhaps as a concise reference article a paper of this type does serve a useful purpose.

Some consideration of the important malignant tumor of children—retinoblastoma, and its differential diagnosis would have been worthwhile.

I would like to have seen the author take the opportunity to stress the importance of specific diagnosis of external ocular inflammations, and the dangers of the improper use of antibiotic and steroid preparations. The ophthalmologist is well aware that some pediatricians and general practitioners treat any external eye disease initially with an antibiotic-steroid preparation as a universal remedy. This drug combination must not be a substitute for judicious clinical judgment. It seems that the ophthalmologist cannot reiterate often enough the role of local steroid therapy in the development of or enhancement of serious herpetic and fungal corneal infections. A few basic rules concerning the use of antibiotics also needs repeated emphasis: use antibiotics only when indicated (if diagnosis is not certain a trial of less hazardous drugs such as zinc salts or detergents is warranted); attempt to select the proper antibiotic, preferably one that has a low sensitizing action (most of these antibiotics are not used by the pediatrician for systemic use because of their toxicity); avoid prolonged use of antibiotics to prevent the overgrowth of resistant organisms and fungi.

Too often the conscientious pediatrician is faced with the dilemma of when to take care of a child's eye problem and when to call an ophthalmologist. Having previously been a pediatrician I can well appreciate this feeling. On the one hand the ophthalmologist (I refer not only to this article) tells the pediatrician that he can and should take care of simple injuries and diseases of the eye. On the other hand the ophthalmologist warns the pediatrician that serious eye diseases may be subtle in their gross external manifestations (*e.g.*, small subconjunctival hemorrhage but a retained intraocular foreign body or retinal detachment), or he shows the pediatrician a notched eyelid that had been improperly sutured. Frequently in ophthalmic articles written for the pediatrician he is made to feel incompetent if after reading the article he cannot take care of a number of eye disorders. The attempt to separate "simple injuries and diseases" or minor surgery from "serious injuries and diseases" or major surgery is fraught with danger. Often simple problems become major ones through carelessness or incompetence. When it comes to the care of eyes fortunately most pediatricians realize their limitations and promptly refer the patient to the ophthalmologist if one is reasonably close. This may mean over-referrals but in the long run the pediatrician and ophthalmologist are satisfied, and the patient gets the best care.

LEONARD APT

Space Ophthalmology

TIME, SPACE AND STEREOSCOPIC VISION

STANLEY DIAMOND

Aerospace Medicine, 1959, *30:* 650–663.

In flight at very high speeds, rapid depth perception is highly important, and stereoscopic vision is a known factor in depth perception. Stereoscopic vision is limited in time as well as space and involves distance scotoma, or the time interval in which visual perception cannot be achieved.

Stereoscopic vision employs binocular parallax to determine depth. The stereoscopic threshold, the minimum parallax angular differences of 2 objects at unequal distances from the observer, averages about 2 arc seconds. This will vary, owing to subjective factors. The threshold increases (deteriorates) with decreasing exposure time of the objects.

The range of stereoscopic vision depends on the threshold and interocular distance. For a pilot approaching objects at unequal distances, near and far objects can be discriminated in depth (within the time limit through which he approaches) so long as the far object is within stereoscopic range. This range R is given by the equation, $R = p/d\theta + pD$), where p is interocular distance, $d\theta$ is minimum parallax angle difference (stereoscopic threshold in radians), and D is the fixation distance to the far object.

Theoretical ranges for true stereoscopic vision decrease with approaching finite fixation distance D and with increasing threshold $d\theta$. The ranges are greatest between 2 and 7 arc seconds and vary from 4,000 to 650 meters with a D of 10,000 meters to 850 to 450 meters for a D of 1,000 meters as threshold values change from 2 to 20 arc seconds. Stereoscopic vision begins when a far object is bifoveally fixed and fused. At this point, an interval of stereoscopic range exists, divided into 3 time increments: minimum depth perception time (MDT), reaction time (RT), and maneuver time (MT).

The MDT is variable but seems to lie between 1.5 and 3 seconds; of this time 1 second is needed to attain optimum threshold. The MDT is affected by pilot anticipation, visibility, empty-space myopia, and high acceleration, among others. In this study, on the basis of the calculated values and clinical evidence, 2.5 seconds was used as the average MDT. The aircraft will fly through the stereoscopic-vision range in the stereoscopic time-distance interval (STD). As speeds increase, the STD interval will be taken up by the MDT. For example, assuming an MDT of 2.5 seconds at a speed of Mach 2 (1,520 mph) and a D of 5,000 meters with a threshold of 4 arc seconds, the STD interval is only 3

seconds, which allows only 0.5 second for depth perception, pilot reaction, and maneuver.

There is a critical range limit and corresponding critical closure speed within the stereoscopic range-time. These are calculated to average 554 meters and 495 mph, respectively In excess of these values, stereoscopic vision will be useless. (This applies to stereoscopic range-time; monocular or other factors may permit extension of these values.)

These findings indicate that stereoscopic vision is of limited value in flight at present high and future high-supersonic speeds, although it is useful in low-rate-of-closure situations such as landings and takeoffs, formation flying, collision courses with small relative heading angles, and so forth. The critical closing airspeed for depth-range, exclusive of reaction and maneuver times, may be held to 400 to 580 mph owing to human visual limitations. Keener thresholds and longer ranges appear to be necessary at speeds between 2 and 3 times the speed of sound; they may possibly be obtained by optical and electro-optical devices, although their feasibility is limited. At higher speeds, the primary value of stereoscopic vision is most questionable. It is foreseen that electronically-controlled depth- and distance-control systems in high-performance aircraft may well be necessary to insure maximum flight safety at very high speeds.

Comment: This is an interesting article. It again emphasizes the fact that there are certain "built-in" delays in man's neurologic system which, coupled with the known limits in sensitivity of some visual functions, serves as a limiting factor in the performance of the man-machine system. If maximum performance and maximum safety are desired, this represents another area in which electronic assistance for the man will be required. It considers only stereopsis, however, which is just one of the factors involved in depth perception. Other factors are frequently more important in distant depth discriminations and, under many circumstances, will increase the distances at which temporal relationships can be established visually.

VICTOR A. BYRNES

Basic Sciences

PHARMACOLOGY

ATROPINE POISONING WITH PSYCHOSIS

MARIA EMMA GAMBOA AND EDWARD W. GAMBLE, III

A. M. A. J. Dis. of Child., 1959, *97:* 104

A report is presented of a rare case of atropine poisoning which resulted in a predominance of mental symptoms, with complete absence of the more usual physiologic manifestations.

A dosage of 1 per cent atropine, 2 drops in each eye three times a day, was prescribed for the patient, a 10-year-old, mentally retarded, Negro boy with a diagnosis of alternating esotropia. Within 2 days he developed a psychotic reaction, with visual hallucinations, hyperexcitability, behavioral disturbance, and personality changes which were manifested in psychologic tests. He did not have fever, gastrointestinal disturbances, or other signs of atropinism. Neurologic examination revealed enlarged, fixed pupils and deep tendon hyperreflexia, but there were no other significant physical findings.

Two possible causes for the reaction were considered: (1) a superimposed schizophrenia in a retarded, birth-injured child; and (2) an acute intoxication due to atropine drops. A provisional diagnosis of acute psychotic reaction to atropine was made, and chlorpromazine (Thorazine) was prescribed. The absence of mental signs after 22 days, as revealed by both psychiatric and psychologic examinations, led to the conclusion that the condition was an acute intoxication from atropine, incurred, in spite of the small dosage prescribed, by a patient who had increased susceptibility or idiosyncrasy to this drug.

Comment: Ophthalmologists are no doubt aware of the possibility of mental symptoms occurring in association with atropine poisoning. The literature is documented with such individuals, but we may have a tendency to forget this in ordering the agent for routine cycloplegic examination. It is imperative that parents be warned of this possibility, so that proper therapy can be instituted. It is necessary that this be done when atropine is used locally as a therapeutic measure.

IRVING H. LEOPOLD

MICROBIOLOGY

INTRA-OCULAR COENURUS INFESTATION

E. Epstein, N. S. F. Proctor and H. J. Heinz

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South African M. J., 1959, *33:* 602–604

Coenurus is the term applied to the cystic larval stage of a tapeworm in which there are numerous scolices in contrast with cysticercus, and no evidence of daughter cysts as in hydatid. This particular larval form, as well as the characteristic shape of the rostellum and hooklets and certain features of the vagina in the adult worm, are considered diagnostic systematic traits of the subgenus Multiceps. The proper host of the adult worm of a number of species of Multiceps is not known, but it is safe to say that various carnivores, especially canines, harbor it. Intermediate hosts may vary greatly. The greatest number are to be found among the rodents, but various primates have been incriminated.

Multiceps coenurus (coenurus cerebralis) has a wide host distribution. Though it is most frequently reported as inhabiting the central nervous system, coenurus occurs in animals in the intermuscular connective tissue, the abdominal cavity, the thoracic sheath, and the pericardial sheath. Many human coenurus infestations are doubtlessly passed off as hydatid cysts.

The present case, which illustrates the value of a surgical exploration of the uveal tract, is only the third case on record of an intra-ocular coenurus infestation. It concerned a female European child aged 3½ years. She was born in the Transvaal but for the year before consultation had been resident in Swaziland. The mother had noticed that during the previous 2 to 3 months the left eye had been variably congested and that at times the child complained that it was sore. The patient's doctors had treated her for conjunctivitis.

Examination showed a mildly flushed eye, a small clotted streak of blood on the iris, and a few delicate posterior synechiae. The vitreous was very hazy and fundal details could not be seen, but it was obvious that a white raised mass was present on the nasal side. The tension of the eye was normal. Good mydriasis revealed that an extensive smooth high elevation of the nasal fundus was present, reaching from the ciliary body to apparently the region of the disk, although it was extremely difficult to define the disk on account of the vitreous haze. The swelling tapered off below and above the horizontal meridian, between the ora serrata and the equator; the retina appeared flat in the oblique meridians although it had the same edematous whitish appearance as on the

swelling itself. No movement was noticed in the mass, which was especially examined for this phenomenon.

The findings suggested a granulomatous uveal inflammatory lesion and, among the possible causes, tuberculosis, Coats's disease, cysticercosis, hydatid disease and even hookworm infestation were considered. Neoplastic disease was excluded as unlikely on the physical findings.

Surgical exploration of the mass was considered at least for biopsy to pave the way if possible for rational therapy. The region corresponding with the maximal swelling in the fundus was gently incised, and suddenly a small white cystic mass herniated through the incision. The whole simulated a typical cysticerus cellulosae. With this assumption in mind a pair of iris forceps were applied with closed blades to sweep the cyst from the wound in the choroid.

The cyst was about 8 mm. in diameter but of rather irregular shape. Numerous white nodules of about 1 to 2 mm. in diameter were clearly visible in the wall of the cyst; fresh preparations showed these to be definite scolices. The individual scolices consisted of a rostellum with a double row of hooklets and four suckers typical of the taenia type of tapeworm. There were no daughter cysts.

Four months after the operation the disk was still red, but there was apparently no return of vision, although the pupil reacted a little to light. Cosmetically, however, the eye appeared normal. Unfortunately follow-up was limited to 6 months, when contact was lost. It is probable that this child was infected from the ingestion of eggs passed in the stools of an infected dog, but attempts to trace the infection proved fruitless.

Comment: This is a very interesting case report which is well documented with evidence which substantiates the diagnosis of this rare cestode infection. The absence of an increase in the eosinophil percentage in the case reported in this paper indicates that one should not exclude the possibility of helminthiasis when there is no eosinophilia. Another helminthic infection which should be considered in the tentative diagnosis of appropriate eye lesions is visceral larva migrans, commonly caused by an ascarid of dogs, *Toxocara canis*.

GEORGE M. HAIK

BIOCHEMISTRY

THE BIOCHEMICAL STUDIES ON PIGMENTARY DEGENERATION OF RETINA (RETINITIS PIGMENTOSA)

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Keio J. Med., 1958, 7: 61–74

Pigmentary degeneration of the retina (P.D.R.), or retinitis pigmentosa, is a chronic inflammation of the retina with atrophy and pigmentary infiltration of the inner layers. Although many cases have been reported clinically and pathologically, the pathogenesis of this disease is still unknown. Levy-Wolff expressed the opinion that it might be caused by arteriosclerosis associated with dysfunction of the tuber cinereum of the third ventricle. Kandori, Fujinaja and others reported that the disease is based on a dysfunction of the anterior lobe of the pituitary gland. Others have associated it with disorders of the central nervous system. From the pathologic point of view it is considered a degeneration of the blood vessels of the choroid and retina with hyaline and endovascular obliterating changes which might be related to lipoprotein and mucoprotein metabolism.

The present study reports the results of biochemical studies made in the author's laboratory on the liver function, lipid metabolism and lipoprotein-mucoprotein metabolism of patients with P.D.R.

Experiments on Liver Function (Serum Colloidal Reactions in P.D.R.). The subjects were 10 patients with retinitis pigmentosa. The tests used were: (1) Takata-Ara's reaction, (2) Sawada-So's reaction, (3) the bobalt reaction, (4) Maclagan's thymol turbidity test, (5) Neefe's thymol flocculation test, and (6) Hanger's cephalin cholesterol flocculation test. These tests are used to determine the presence of abnormal protein constituents in the blood serum. The first three measure the relative increase in the amount of globulin to the amount of albumin. The thymol procedures are based on the production of turbidity within 30 minutes by serum added to a saturated buffered thymol solution. The cephalin cholesterol flocculation test is based on the capacity of serum from patients with liver disease to flocculate a colloidal cephalin cholesterol suspension. Positive reactions were obtained in 7 of the Takata-Ara's tests, 1 of the Sawada-So's tests, 9 each of the cobalt, thymol turbidity and thymol flocculation tests and 4 (of 5) of the cephalin cholesterol tests. The reactions were similar to those obtained in liver disease, but to a lesser degree. It is assumed that latent functional disorders of the liver are found in P.D.R.

Experiments on Lipid Metabolism. The author determined the cholesterol and phospholipid levels in the blood serum of 22 P.D.R. patients ranging in age from 5 to 72 years. Saifer's method was used for the cholesterol determinations

and Gomori's procedure for phospholipid. The total cholesterol levels (130 to 254 mg./dl.), esterified cholesterol fraction, and the phospholipid levels (× 25 mf./dl. = 130 to 144), were all within the normal range. The cholesterol-phospholipid ratios (0.8 to 1.28) were lower than the normal average, indicating a relative increase in phospholipid in comparison with cholesterol. These findings do not support the view that the development of atherosclerosis is associated with high concentrations of cholesterol and led the author to the consideration that other factors, such as the storage of lipids in the cells of the central nervous system, may be involved in the production of the atherosclerotic changes seen in the retinal vessels of P.D.R. patients.

Experiments on Lipoprotein and Mucoprotein. Barr and his associates reported that atherosclerotic subjects tend to have an increase in the concentration of β-lipoprotein and a decrease of α-lipoprotein. By use of the paper-electrophoresis method, the author found that both α-lipoprotein and the β-lipoprotein concentrations in the serum of 20 P.D.R. patients, ranging in age from 10 to 72 years, were in the normal range, and the ratios of β- to α-lipoprotein (1.6 to 2.8) were also normal. The ratios of α- to β-mucoproteins (0.60 to 1.76), also determined by paper-electrophoresis, were found to be correlated to obliterating changes of the retinal arteries.

On the basis of the results of these studies the author considers the possibility that P.D.R. may be one of a group of diseases of tapetoretinal degeneration without dementia due to faulty metabolism of fat, with resulting storage of lipid in the cells of the central nervous system.

Comment: The pathogenesis of so-called retinitis pigmentosa and of other related hereditary ocular diseases has always been a mystery. A genetic factor is generally accepted. The biochemical changes leading to or associated with the manifestations of the disease are largely unknown. Animal experiments have provided some evidence that the inhibition of certain enzymes by chemical agents like monoiodoacetate or ionizing radiation may produce retinal lesions which, from a clinical and histologic viewpoint, resemble closely those observed in pigmentary degenerations. The experiments reported by Sakanoue suggest that systemic abnormalities may play an essential role or are associated with the retinal degenerations. These include alterations in liver function tests and in serum manifestations. His evidence is far from convincing, however, and it is the opinion of the reviewer that the primary alterations may take place in the pigment epithelium or choriocapillaries as well as in the perceptive elements of the retina. The retinal changes may be entirely or partly secondary in nature.

PAUL A. CIBIS

RECENT ADVANCES IN THE CHEMISTRY OF THE CEREBROSPINAL FLUID

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J. Nerv. & Ment. Dis., 1959, *127:* 359–373

In recent years there has been a major revision in our concepts about the formation of cerebrospinal fluid. CSF is not only an ultrafiltrate formed by way of the choroid plexuses in the ventricles, but is also the product of an exchange between the blood and the central nervous system at all levels of the subarachnoid space. The CSF appears in a state of dynamic equilibrium, not just with the blood, but also with the interstitial fluid of all parts of the central nervous system. Thus it is in a unique position to reflect such changes in the properties of neural tissue as may occur in disease. The application of modern laboratory techniques, such as electrophoresis, chromatography, spectroscopy, and flame photometry, to the investigation of the CSF has yielded a better understanding of neurologic diseases, as well as information of practical value in their diagnosis.

The present review attempts to inform the reader in a comprehensive manner of the many recent investigations of the CSF, and to evaluate these in terms of their clinical importance.

Electrophoretic separations of the CSF proteins require the concentration of large amounts of fluid. This is necessary because of the low total protein content of the CSF, which rarely exceeds 2 per cent, even in disease. The γ-globulin of the CSF rises proportionately as the total protein increases. However, when it exceeds 13 per cent of the total protein, this is considered especially significant for the diagnosis of multiple sclerosis or neurosyphilis. The γ-globulin must always be considered in relation to the total protein. Evaluations are of greatest diagnostic value when the total protein is normal.

The identification and quantitative estimation of the free amino acids in CSF was made possible by the development of paper chromatographic techniques. Aspartic, glutamic, and aminoacetic acids were identified, as well as serine, threonine, glutamine, alanine, tyrosine, valine, phenylalanine, and leucine in many specimens. Less frequently found were γ-aminobutyric and α-aminobutyric acids, histidine, lysine, asparagine, cystine, and arginine. Of all these compounds, glutamine was present in the highest concentrations.

Several investigations of CSF cholinesterase have been conducted, motivated by the physiologic importance of this enzyme in neural transmission. Both true and pseudo-cholinesterases have been found in human CSF, but unlike the serum, the true or β-methylcholine hydrolyzing cholinesterase constitutes the major fraction. A critical evaluation of the enzyme studies requires a consideration of the methodology used in these various investigations. Regardless of which enzyme is determined, and the method used, the results should be re-

producible, if the necessary conditions described in the method are fulfilled. Many of the reports on CSF enzymes do not define the type of the activity curve. Several investigators have used CSF obtained from pneumoencephalographic studies, assuming that subarachnoid air injections do not influence the CSF enzyme levels. The author has shown that marked elevations of GOT and LDH activity may be ascribed solely to this procedure.

Changes in the blood-brain barrier for enzymes which have a high ratio of serum to CSF activity may occur, but would hardly explain the occasional elevations of serum activity observed in these cases. The lack of correlation between enzyme activities and the protein content of the CSF, in vascular and neoplastic diseases of the central nervous system, does argue against a hematogenous origin of the enzymes.

The total polysaccharide (bound to protein) content of the CSF was increased in multiple sclerosis, neurosyphilis, cerebral thrombosis, symptomatic epilepsy, infectious polyneuritis, and in brain tumors. It is difficult to interpret the increased polysaccharide content of the CSF in various neurologic disorders. Changes in the polysaccharides may reflect changes in the protein fractions to which they are bound. Since the polysaccharides are largely bound to the β-globulin fraction, it is not surprising that both members of this complex are increased in the CSF of brain tumor patients.

Cholesterol and cholesterol esters are present in normal CSF. Increased concentrations of these steroids have been found in neurologic diseases. Oxyhemoglobin, methemoglobin, and bilirubin are the pigments which commonly occur in CSF. Oxyhemoglobin can usually be identified spectroscopically in the lumbar CSF within 2 hours after a cerebral hemorrhage. Bilirubin is present from the third or fourth day until the second or third week. The xanthochromia of CSF which occurs with spinal subarachnoid block is probably due to bilirubin.

When the CSF potassium ion concentration is altered experimentally, serious physiologic disturbances result. It is not surprising that this concentration is maintained within narrow limits. Br^- enters the CSF more slowly than Cl^-, and reaches much lower concentrations. This ion later re-enters the blood against a concentration gradient. Certain general deductions can be drawn concerning the CSF electrolytes. Ions such as K, Ca, and Mg which are known to profoundly influence neuronal conductivity, are closely regulated in their CSF concentrations. The concentrations of all three ions, relative to each other, are different in the CSF than in the serum. This may have some special implications in regard to neuronal function.

The close cooperation of the clinical neurologist with the research biochemist should assure the accumulation of new data. However, progress is dependent also upon the supply of CSF furnished by all physicians who have the occasion to perform a lumbar puncture. Rather than discarding the surplus CSF removed, the clinician is urged to send it to a research laboratory. He will thus further research which will ultimately benefit him in the diagnosis and management of patients with neurologic diseases.

INFLUENCE OF SODIUM IODATE UPON THE PHOSPHATASE AND LIPASE IN THE RETINA

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J. Jap. Ophth. Soc., 1959, *63:* 575–579

The purpose of these studies was to investigate the activity of acid phosphatase, alkaline phosphatase and lipase as related to the mechanism of denaturation of the retina by sodium iodate. Albino rabbits were given intravenous injections of 30 mg. of sodium iodate per kg. of body weight. The phosphatase analyses were done by the methods of Shimizu and Yukin and of Mashima, and the lipase analyses by the method of Hattori.

Alkaline phosphatase. Histologically it was observed that the alkaline phosphatase activity decreased in the inner layer and the optic cells at first but then increased by the 4th day. Between the 4th and 10th day destruction of the outer layer occurred but the strong activity of the enzyme was still observed in the granules at 10 days. From quantitative measurement, most activity seemed to occur on the 3rd and 7th days with respect to alkaline and neutral phosphatase, but otherwise there was no change in either direction.

Acid phosphatase. Activity was observed in the outer layer granules on the 2nd day. By the 4th day part of the optic cell had been destroyed but the activity in the other layer increased. On the 10th day the enzymatic activity of the node cell was stronger than that at the 2nd day despite the decline of the outer optic cells. The quantitative results were compatible with the histologic observations. Experiments *in vitro* indicated that the activity decreased in the optic cells, the reticuloendothelial layer and nerve layer.

Lipase. A 5 per cent solution of sodium iodate was administered intravenously to the rabbits. Before injection the lipase level was 5.58. On the 2nd, 4th and 6th days it remained at approximately 7.4 and increased to 8.6 on the 8th day. These changes were similar to those of acid phosphatase. It appears that the increase in lipase is due to the destruction of tissue, inhibition of glycolysis and loss of lipid material by the iodate and is thus compensating for the changes of the cell activity caused by the drug. It has already been shown by Ota and Nakamura that sodium iodate causes temporary decrease of glycogen, increase of the PAS reaction in the retina and inhibition of glycolysis.

Since histochemically the increase of the acid phosphatase activity corresponds to an increase of nucleus activity, as well as being related to the enzymatic activity of nerve fiber and the reticulocyte system, it is understandable that the acid phosphatase activity increased with the destruction of the outer node where a large amount of lipid material is found. The inhibitory effect on the

glucose metabolism in this layer is probably related to the increased activity of the acid phosphatase by the administration of sodium iodate. A similar increase was observed by Kojima and Hagaya after the administration of carbon tetrachloride. It thus appears that the node cells are the main site of glycolysis in the metabolism of the retina.

Comment: An evaluation of the report is hampered by the lack of a precise and consistent use of terminology.

It appears to me, that the observations reported in this paper are important, insofar as they provide evidence that, in rabbit, sodium iodate intravenously injected at doses of 30 mg. per kg. of body weight affects not only the outer layers of the retina, but also the inner layers. This can be inferred from the fact that alkaline phosphatase decreased in its activity during the first 3 days after the injection, but increased between the 4th and 10th day, although destruction of the outer layers advanced at the same time.

Acid phosphatase activity in the outer layers vanished after 2 days, but increased in the inner layers.

The changes of lipase activity concurred with the destruction of tissue in the outer layers, the inhibition of glycolysis, temporary decrease of glycogen, and the increase of PAS-reaction (Ota and Nakamura). The effect of sodium iodate on the pigment epithelium has not been discussed. It would be of interest to know how these histochemical findings correlate to functional changes induced by sodium iodate, *e.g.*, alterations of the ERG, as reported by Noell, and whether the same or similar changes occur in the retina of other species, particularly mammalians.

PAUL A. CIBIS

ANATOMY

STUDIES ON THE STRUCTURE OF THE VITREOUS BODY AFTER REFRIGERATION WITH CARBON DIOXIDE ICE

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Acta Ophth., 1958, *36:* 929–939

Knowledge of the biochemistry and biophysics of the vitreous has greatly increased in recent years, yet the problem of the existence of a framework within the vitreous and of its properties has not been fully solved. Although some workers were unable to find any structure in the vitreous, most authorities within the last several years have been able to demonstrate by various methods, *e.g.*, histologically and biomicroscopically, by ultra phase contrast and electron microscopy that the vitreous does actually possess a fibrous or membranous structure, or both.

The histologic study of the vitreous has proved very difficult. The fibers and membranes it may contain are easily destroyed by fixation and staining. Consequently, the fibers and aggregates seen in the section are not necessarily connected with the original framework. It is not surprising, then, to find that the opinions contained in the literature about the localization and character of the structure of the vitreous vary to some extent. The difficulties encountered in the histologic examination of the vitreous are paralleled by those met with in its biomicroscopical study, *e.g.*, through slight magnification, continuous motion of the vitreous, and the fact that it is difficult to explore the posterior vitreous of the living eye for optical reasons. To overcome these difficulties, the authors examined the structure of the solid vitreous in the bovine eye after freezing with carbon dioxide ice. The frozen vitreous was examined both macroscopically from magnifications of photographs × 15 and microscopically at magnification of × 100 and × 200. The frozen eyes were cut in two and the inner surfaces of the halves were polished to a mirrorlike smoothness with very fine grinding papers.

Cloquet's canal became visible in the congealed vitreous if the line of intersection ran through the optic disk. The frozen vitreous was more closely attached to the bulbar wall at the sites of the ciliary body, the equator, and the optic disk, and more loosely near the macula. In some eyes there were points of slight adhesion between the optic disk and the equator. From the photographs, it could be seen that the fibers ran from the ciliary body and from the points of adhesion mainly in two directions, *i.e.*, to the center of the vitreous toward Cloquet's canal and toward the next point of adhesion. In the area of Cloquet's canal the course of the fibers was that of the canal itself. The zonule formed a group of fibers which was distinct from the rest of the vitreous.

In the microscopic examination a netlike framework composed of fibers could be seen in the vitreous, in the center of which the fibers of the framework seemed to be finer and the meshes of the net larger. In the opinion of the authors, these fibers are real and not merely aggregations of fibers. While freezing to minus 50°C. may produce artifacts, if the freezing of these eyes had altered the framework of the vitreous, it would hardly have been possible to bring out such fine fibrous network, unbroken zonules, and Cloquet's canal with its fibers. Moreover, the size, localization, and course of the network fibers are approximately in agreement with the slit lamp findings.

Comment: Progress in any branch of science occurs in a series of jumps often occasioned by the application of new methods to an old problem. The structure of the vitreous humor has been very difficult to determine by classical methods for reasons set forth above. Oksala and Lehtinen have used a method taken very largely from petrography which has been successful in revealing the microscopic structure of minerals. Such a seemingly unlikely technique to apply to the softest tissue was made successful by freezing the vitreous to a rock-like hardness so that polished surfaces of gross sections could be made. By use of this and other techniques, we are brought to the realization of a genuine structure of the vitreous as a whole. Heretofore only glimpses or suggestions of such a structure were available. Knowledge of this anatomy is of practical value in relation to the distribution of nutrients in the normal; blood cells following hemorrhage and in retinal detachment. This study fortifies data obtained *in vivo* by slit lamp examination and offers considerable advantage over microscopic examination of small pieces in which the relation of the fragment to the gross structure is not apparent.

G. K. SMELSER

Miscellany

RESEARCH

EYE RESEARCH IN CANADA

J. H. Grove,* M.D.

M. Services J. Canada, 1959, *15:* 390

Little eye research was done in Canada until recent years as the circumstances were not favourable. Prospective ophthalmologists had to go outside of Canada to obtain training in the specialty, and those ophthalmologists who were interested in or qualified to do research were handicapped by lack of funds and facilities.

The situation began to change in 1946 when Dr. W. W. Wright organized the first Canadian post-graduate course in ophthalmology at the University of Toronto Medical School. (Some years later, similar courses started at the University of Montreal, McGill, the Universities of Saskatchewan, Alberta and British Columbia.)

With the training of ophthalmologists underway at Toronto, it was a logical step to consider starting eye research there. A main hindrance was lack of finances. This problem was solved, up to a point, when funds became available for research under the National Health Grants program which was inaugurated in 1948 by the Department of National Health and Welfare.

Dr. A. J. Elliot who succeeded Doctor Wright as Head of the Department of Ophthalmology had, on his staff, several ophthalmologists who were qualified by training and scientific background to conduct eye research. Advantage was taken of the Health Grants to make use of the services of these ophthalmologists.

In 1950, research was begun by Dr. H. L. Ormsby into virus eye diseases and by Dr. T. H. Hodgson into certain aspects of glaucoma. Both doctors were fortunate in securing the services of highly trained research associates. Equipment was purchased and laboratory space was generously supplied by the Banting Institute.

The glaucoma project was productive of important information concerning aqueous outflow. Doctors Hodgson and R. K. MacDonald developed a new method of corneal-scleral tenography. Further investigation of glaucoma is continuing.

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The virus project of Doctor Ormsby was completed last year. Much new information had been obtained concerning tissue culture, the identification of viruses which infect the eyes, and the treatment of these infections. A number of papers by Doctor Ormsby and his colleagues have appeared in the Medical Journals attesting to their outstanding work. New research projects have developed out of the original virus project dealing with diseases and biochemistry of the cornea, corneal transplantation and preservation of donor cornea material. This research is continuing. A research Eye Bank was set up and experience gained therein has enabled the Canadian National Institute for the Blind to organize Eye Banks in Toronto, Montreal, Winnipeg, Edmonton, Saskatoon and Vancouver.

At the Charles H. Best Institute, Doctor H. R. Hausler has commenced research into diabetic retinopathy.

Several years ago, Dr. A. L. Morgan, Head of the Department of Opthalmology at the Hospital for Sick Children, Toronto, obtained grants for research into the causes and therapy of strabismus and infantile glaucoma. This work is continuing and improved methods of treatment have already been developed. At the same hospital, a project is commencing to investigate newer methods of treating amblyopia in children.

In all these Toronto projects, opportunity is being given to the ophthalmologists in training to take part in the research. Several of these doctors, after completing their course in ophthalmology, went to England or the U.S.A. to do further eye research. They have now returned to Toronto and are working as research associates in the Toronto projects.

At the Montreal General Hospital, a retinal detachment clinic has been set up by Dr. S. T. Adams under a grant. In addition to providing therapy, Doctor Adams is teaching the newer methods of treatment to post-graduate students and to ophthalmologists. At the same hospital, Dr. R. J. Viger, director of the Glaucoma Clinic, in addition to evaluating new methods of treatment is gathering important statistical data concerning the incidence of glaucoma. There are now 10 Glaucoma Clinics financed by the Health Grants program situated in the following cities: Saint John, N.B., Quebec, Montreal (3 clinics), Toronto, London, Ottawa, Winnipeg, and Saskatoon.

In Saskatoon, Dr. R. G. Murray is directing research into glaucoma in connection with the Glaucoma Clinic there.

Research eye projects under the grants are being planned for other Montreal Hospitals.

Considerable eye research is also being done under other auspices than the National Health Grants Program. At Kingston, Dr. D. Rosen is investigating aqueous outflow under a grant from the National Research Council of Canada. Under grants from the Defence Research Board, Dr. Clement McCulloch of Toronto, Chairman of the Visual Panel of the Board, is investigating cataract formation due to thermal radiation, and Dr. R. D. Burns, physiologist of Montreal, is doing basic research into the functional organization of the mammalian visual system. Also at the Defence Research Board Medical Laboratories at

Toronto, Dr. J. Ogilvie is investigating the effect of orientation on the visibility of fine wires, and Mr. P. Foley has published a paper on the determination of some parameters of effective visual background. These psychologists are also engaged in other visual research.

A number of Canadian ophthalmologists, on their own responsibility have completed, or are engaged in various phases of eye research and visual problems. In Montreal, Dr. J. V. V. Nicholls has done considerable eye research, including investigations of the visual problems of aviators and motor car drivers. Retrolental fibroplasia first began to appear about 15 years ago in premature infants and quickly became the commonest cause of blindness in children. Ophthalmologists were puzzled because cases were much more frequent in some hospitals than in others. Norman Ashton of England showed in animals that excess oxygen was the main cause of the disease. At the same time, Dr. J. C. Locke, now head of the Department of Ophthalmology at McGill, was doing clinical research into causes, prevention and treatment of the disease. After extensive investigations Doctor Locke demonstrated that the disease can be completely prevented by proper limitation of the amount of oxygen given to premature infants in incubators. In recogition of this achievement, Doctor Locke was given in 1954 the Annual Award in Medicine of the Royal College of Physicians and Surgeons of Canada.

In Vancouver, Dr. Derek Simpson and colleagues after extensive investigation produced standards for the visual efficiency of motor car drivers.

Various other ophthalmologists in Quebec, Montreal, Toronto, Winnipeg and Vancouver are also engaged in various aspects of eye research.

Most of these eye research projects including those under the National Health Grants are being directed by ophthalmologists who spend part of their time in private and hospital practice. In this way, the research is not divorced from its practical application in therapy. The research associates include several full time ophthalmologists and a number of research workers with Ph.D. qualifications or the equivalent. At the next annual meeting of the Canadian Ophthalmological Society a session will be held for the presentation of research papers by Canadian ophthalmologists.

It can be seen that eye research has become an important factor in Canadian ophthalmology. Leading ophthalmologists as well as the Canadian National Institute for the Blind point out the need for an eye institute similar to those in all other countries which have modern medical facilities. In such an institute eye research could be coordinated and carried out on a permanent basis and special treatment services could be provided.

PREVENTIVE OPHTHALMOLOGY

AN EYE CONSERVATION PROGRAM FOR LARGE AND SMALL INDUSTRY

J. H. GANSCHOW

Detroit, Michigan

J. Iowa M. Soc., 1959 *49:* 505

A highly successful eye-protection program was initiated in the Detroit-Chevrolet Gear, Axle, and Forge plants which involve a wide range in manufacturing tools, skills, and conditions. The program consists in the wearing of safety glasses by all personnel, and is added to any special devices which may be necessary in particular situations.

Most occupational injuries affect the musculo-skeletal system and leave no permanent disability, but even slight injuries to the eye may impair function or may lead to gradual changes which seriously impair vision. When we depended on voluntary use of glasses, even capable and otherwise cooperative skilled men chiseled on the eye-protection program. It therefore appeared to be necessary to insist on wearing glasses, and to use a disciplinary system if necessary.

Since their cooperation was important, supervisors received the first glasses, and the program was then extended until all men in the factory used them. Scattered objections disappeared quickly, the safety department gained in prestige, and management-labor relations improved.

Well fitted and adjusted standard safety glasses of good quality, resembling those worn by the general population, are the best for most purposes, adding refinements when necessary. These glasses are issued as personnel equipment to everyone who enters the plant. If a man forgets or looses a pair, he can obtain others through the personnel department, and replacements and repairs are obtained through the safety office. Tissues for lens cleaning are distributed in dispensers throughout the factory. A person capable of fitting and adjusting glasses visits each factory every week, and fitting and repair services are always available in the safety office. Good maintenance is important.

About a year and a half after introducing the safety program the company also undertook to supply prescription glasses. The employee takes an explanatory letter and prescription blank to his own ophthalmologist, and the prescription is filled by a large optical company in safety glass in standard frames.

In order to evaluate results, the compensation department and medical department records were reviewed. Between 1923 and June 1, 1958, compensation payments were made for 177 eye injuries, 63 of which involved loss of vision in one eye. In 83 per cent of the injuries causing blindness and in 81 per cent of the others, the injury was caused by small foreign bodies, usually tiny, high velocity, metal particles produced by impact of two hard surfaces or by sudden

stress or breakage of such surfaces. Descriptions of the accidents showed that all but 18 might have been prevented by safety glasses. We also found that 11 eyes were lost during a period before institution of the safety program which was of the same duration as that of the safety program, whereas only 1 eye had been lost since that time. Moreover, this one injury was of a type which could hardly have occurred if the man had been wearing his safety glasses. In one other instance compensation has been paid for eye injury since the program went into effect.

Moreover, there has been a drop from about 100 minor eye injuries a year to between 6 and 22. Apparently injuries do not correlate with age, shift worked, type of work, experience, visual efficiency, or status. Jobs with obvious eye hazards do not produce eye injuries. Including the prescription glasses, the eye protection program costs less than $3.00 per employee a year.

Adaptations of this program are obviously necessary in other types of factories in which the eye accident rate is high. Any program must be based on careful and continuing survey of hazards, on well kept records, and on nurses or other aid personnel who are carefully instructed on the care of slight injuries to the eye. A competent ophthalmologist should always be available. All injuries should be carefully followed.

We have also had incidental benefits following the program. Many employees are for the first time having their eyes examined by ophthalmologists and are having their vision improved by properly prescribed glasses. We have also become interested in the visual fitness of men in jobs requiring close tolerance or men on hazardous jobs such as truck driving. The program has also eliminated unnecessary routine visits to eye clinics, and has reduced the number of claims for inflammatory of degenerative or other eye changes due to employment.

Comment: Dr. Ganschow describes an excellent program and indicates a realistic approach to the problem of reducing eye injuries in a plant equipped with the type of machinery that he describes. He emphasizes the fact that an eye injury is usually much more crippling than any other type of an injury jobwise, which exemplifies my favorite statement that, "we can walk with a wooden leg; we can do things with a steel hand; we can work with a metal brace on our back, but we cannot see with a glass eye." If compulsion is used when and where eye protection is really needed, it pays. If compulsion is used where everyone including the worker, knows the hazard is minimum, there will be resistance and it will fail. A part of the responsibility of industry *is* to indoctrinate their workers on safe home practices bearing out the rationale of eye protection whenever certain jobs are tackled.

Of tremendous importance, and emphasized by Dr. Ganschow, is the fact that supervision must lead the way. Without supervision complying 100 per cent to the rules and regulations, there will be no success. Also I am wholeheartedly of the opinion that the choice of equipment used must be kept simple, standard, meeting all government requirements, and that there is no economy in bargains and only trouble and reaction if some people have something different and special.

In one area, I would like to disagree with Dr. Ganschow. In our experience, it has been found better for the company and everyone else concerned, if the refractions are paid for by the company. If the company pays for them, it is proper and fitting that they

should have a report. Such a report often brings very valuable information to the company with reference to job placement; the necessity for more frequent eye examinations or the knowledge that a man has only one eye. If a man pays for his examination, such a report cannot be requested. In the same category it is our experience that if a man has some stake in his equipment, he takes better care of it and we suggest as a rule, that the company pay for the frames and half or none of the lenses. In this conection, a payroll visual survey also serves the company and the employee. If it has never been done, it can easily be done with binocular instrumentation gradually and on a voluntary basis. This nets immense profit to everyone in discovering new problems and checking on old ones. After such a survey, only key people, operators of mobile equipment, or men with precision jobs, would need to have periodic re-examination. Older people are best included in whom pathology might be suspected.

Union support and cooperation is essential, in fact some of the best programs in this area are policed and promoted by the unions. Such a program could as outlined, be applied in many plants but not every plant. The basic realism of when to apply a compulsory program is of first order. It can however always be applied in departments of a large plant, where the over-all picture might contraindicate a compulsory program.

Good safety and first aid practices are essential. The testing of an individual's visual skills before the dispensing of plant eye protection is also exceedingly important and not brought up by Dr. Ganschow. He has made an excellent contribution.

HEDWIG S. KUHN

RADIOACTIVITY

RADIOACTIVE FALLOUT AND MEDICINE

WILLARD F. LIBBY

New York J. Med., *59:* 1625–1631, 1959

Radioactive fallout is the radioactive debris resulting from splitting of uranium or plutonium atoms by nuclear explosion. This material is incorporated into the dust formed by the explosion. The radiation is either the simultaneous emission of an electron and an antineutrino (β-radiation) or the emission of a γ-ray. β-Rays constitute about one-third of fallout radiation, γ-rays the remainder. The short range, more absorbable β-radiation is able to cause effects only when the fallout is taken internally or is in direct contact with the skin; but γ-radiation is so penetrating that a yard or two of earth or concrete is required for full protection under heavy fallout conditions.

Surface bursts over land can produce a local fallout of as much as 80 per cent of the radioactive material during the first few hours, in a pattern determined by the atmospheric conditions. The particles which are too fine to fall in the first hours eventually descend over a very wide area; this material, termed worldwide or stratospheric fallout, spends an average of about 10 years in the air, thus its radiations are reduced in intensity when deposition finally occurs. A rough rule is that hydrogen bombs are strong enough to push into the stratosphere whereas atomic bombs are not. Tropospheric fallout results when an atomic bomb cloud stabilizes below the stratosphere in the lower atmosphere.

In nuclear warfare the external radiation from local fallout probably would be the principal hazard. The γ-radiation can produce possible effects on health ranging from disabilities noticeable within a few hours after intense exposure (and which may lead to death in a few days) to the induction of leukemia and possibly cancer of the bone, which may appear years later. These measurable health effects are first expected at doses of about 100 r of whole body radiation. Death occurs for whole body radiation in 50 per cent of the cases of exposure at about 450 r. The natural radiation from the ground, our own bodies, and the cosmic rays amount to a total of 0.1 to 0.2 r per year. Exact knowledge concerning genetic effects is not yet known for human beings, but experiments on animals and plants indicate that about 10 per cent of the genetic mutations we have now are due to natural radiation and that the genetic effects of radiation will be proportional to total and cumulative dosage; in other words, there seems to be no recovery from radiation-induced mutations.

Strontium-90, with its very long average life (40 years) and its chemical similarity to calcium, presents the most serious hazard from worldwide fallout. It fixes itself in bone in a semipermanent fashion and can cause cancer of the bone, and also leukemia. It emits no γ-radiation and is therefore not a genetic hazard, since bone structures are not near the reproductive organs. Cesium-137,

a γ-emitter with a high yield, 40-year life, is being seriously watched in worldwide fallout; its effects are the same as for external γ-radiation.

Effective precautions against local fallout are possible, and are matters of public health and medicine. Immediate postattack defense measures include: (1) a national shelter program (remodeling of home basements, building of home and community shelters); (2) a good communications system (transistorized radios, possibly with a built in radiation meter, are essential as there is a period of about an hour or two after a blast during which to take shelter); (3) some means of mobilizing doctors (a specially built automobile that will provide protection against radiation is being considered). Doctors should have radiation meters and know how to read them, because treatment depends on the total dose of radiation received. They should be kept up to date on the latest treatments for radiation injury, and medical supplies (blood for transfusions, glucose for intravenous injections, and antibiotics) should be conveniently available.

In the later postattack phase, contamination of soil with strontium-90 is the major public health and medical problem. Radiostrontium-contaminated calcium in the soil is transmitted into the plant and thus into the human body. If a cow eats a contaminated plant the strontium may reach the body via the milk; but a steer that has eaten contaminated grass puts the radiostrontium in its bone, which humans do not ordinarily eat. Conceivably, therefore, contaminated agricultural farm land could be utilized to fatten cattle for food but for no other purpose. Purification of strontium-contaminated milk is a subject of experimentation at this time, and there may be other ways in other food chains in which the strontium-90 is naturally filtered down.

Further experimentation and thought along these lines are necessary; also essential is the accumulation of vital statistics that will make it possible to estimate more realistically the worldwide hazard from radioactive fallout.

Comment: This article, by the retiring Commissioner of the United States Atomic Energy Commission, should be well received by the ophthalmologic profession. Next to radiology and human genetics, ophthalmology is probably the specialty most conscious of the hazards of radioactivity, particularly since the demonstration by McDonald, Hughes and Pfeiffer, of cataractogenic effects of therapeutic doses of β-radiation which were and still are used widely and successfully in the treatment of external ocular diseases. Well his horizon will undoubtedly be rounded out by the perusal of Libby's lucid, simply worded, but not over simplified treatment of the physical and medical aspects of both the local and the world-wide fallout resulting from atomic explosions.

The ophthalmologic reader of the article will be impressed by the exactness of the physical analysis of the situation and by the comprehensiveness of the radioactivity measurements. The present world-wide fallout from atomic testing, which has been a matter of public concern, was estimated by Libby as 0.005 r per year but is expected to increase sharply during the next 12 months as a result of atomic testing by the Russians in the Arctic zone. This is confirmed by observations of U. S. Naval laboratories which have reported a recent 300 per cent increase of radioactivity in the air at points along the eastern U. S. seaboard (Scientific American, May 1959, Science and Citizen).

TABLE 1

Relation of Dosage of Strontium-90 to Severity of Corneal Damage (Wilson)

No. Representing Strontium-90	Severity of Corneal Damage
35,000	3
45,000	12
60,000	22
65,000	30
83,000	50
92,000	56
Greater than 130,000	80

TABLE 2

Leukemia in Residents of Hiroshima (Official sources)

Distance from Hypocenter (Meters)	No. of Cases of Leukemia		
	With significant radiation	Without complaints	Incidence 100,000/year
Less than 1000	14	2	175.8
1000–1499	15	13	35.2
1500–1999	2	4	4.2
2000–2499	1	1	1.5
2500 or greater	0	8	2.1
Total	32	28	8.1*

* Leukemia incidence in U.S.A. (White) 6.1 per 100,000 per year.

Dr. Libby makes it very clear that all amounts of ionizing radiations originating from atomic bombs and acting on human beings must be viewed against the background of the three unavoidable and inescapable types of radiation on this earth, that is, cosmic rays, earth radiation, and radiation from within our bodies originating from C-14 and K-40. These three sources add up to a total yearly dose of 0.1 to 0.2 r. To this should be added the amount of x-rays to which the average individual is exposed in the course of x-ray examinations and treatments necessitated by disease. The importance of the latter factor is stressed in a recent report of the Morgan Committee (named after the Chairman, Dr. Russell H. Morgan, Radiologist at Johns Hopkins University) which indicts "x-ray machines employed by the health professions as the principle hazard from ionizing radiation" (Scientific American, May 1959, Science and Citizen). "At the present time the most significant source of radiation for the human population is from medical uses," states the radiologist Lester in a recent article on the hazards of ionizing radiations, which makes an excellent companion piece to Libby's article.

The principle difficulty in estimating the potential hazards of these or any amount of ionizing radiations stems from the still very wide gaps in present knowledge concerning the exact relationship between dose and effect of ionizing radiations. Most of the available quantitative data pertain to animals and to large doses of radiation applied during relatively short periods. A case in point is the calibration of β-radiation applicators on the cornea of the normal rabbit (Table 1, from Wilson). In this simple case a roughly linear

releationship obtains between dose of radiation and corneal damage. Data of such quantitative nature can be obtained in man only under most exceptional circumstances. In the population directly hit by the local fallout at Hiroshima, a quantitative relationship between the person's distance from the hypocenter of the bomb and the incidence of leukemia has been established (Table 2, National Academy of Sciences—National Research Council: Report of the Committee on Pathologic Effects of Atomic Radiation, Washington, 1956). Comparable quantitative data have been looked for in vital statistics pertaining to professions with long term exposures to small doses of x-rays. Comparison by March of the death rates due to leukemia of radiologists, on the one hand, and physicians not engaged in the practice of radiology, on the other, have revealed significant differences (4.5 per cent in the former against 0.42 per cent in the latter), but the data do not permit a breakdown into groups according to approximate or estimated doses received. Because of lack of protective equipment, most doses were in excess of 100 r per year and therefore very much in excess of the doses considered in connection with the hazards of current atomic testing.

Dr. Libby rightly stresses the point that the effects of a lack of knowledge regarding the dose-effect relationship may be most serious in the field of radiation-induced genetic defects. There, present-day thinking is very much under the influence of the concept derived from experiments on plants and animals that a certain percentage of genetic mutations now occurring is due to natural ionizing radiation, and that the over-all genetic effect of radiations will be proportional to the total or cumulative dose. Unfortunately, the factor of this assumed proportionality or the dose of radiation for the human population at which the rate of mutations would be doubled (the doubling dose) is not definitely known. From estimates involving a number of assumptions the maximum permissible gonadal dose of radiation, in addition to the natural radiation background, has been set at 10 r during the first 30 years of life. This, as Lester states, "does not preclude an individual's receiving a larger dose if necessary for his health, nor does it mean that this is a non-mutagenic dose." That, to the ophthalmologic reviewer, would seem as rational a conclusion as can be drawn from the present biological and medical data.

Libby's plea for radioactivity measurements by physicians will be well received by those ophthalmologists who have had or are having the opportunity of growing up in or near a modern biochemical laboratory. All ophthalmologists will do well to impress the specific dangers of the local fallout situations firmly on their minds.

PETER C. KRONFELD

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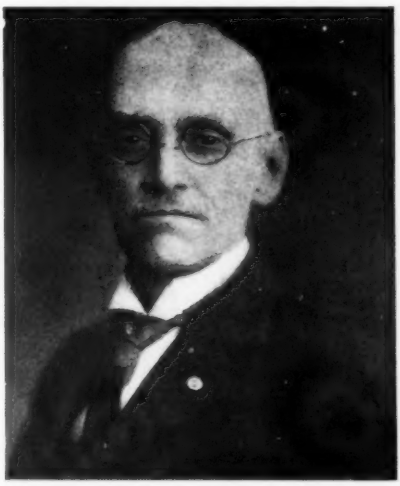
THE CROSSED CYLINDER

EDWARD JACKSON, M.D.

Philadelphia, Pa.

Ophthalmic Record, *2:* 464–466, June, 1893

While this term applies strictly to any combination of cylindrical lenses with the axes perpendicular to one another, it is here intended to speak of such a combination of a convex cylinder and concave cylinder of equal strength, or their optical equivalent sphero-cylindrical lens, as a convex 1 D. cylinder combined with a concave 1 D. cylinder, axes perpendicular; or its equivalent, a



convex 1 D. spherical combined with a concave 2 D. cylinder; or a concave 1 D. spherical combined with a convex 2 D. cylinder.

The advantage of such a lens in the use of the trial set, was referred to at the meeting of the American Ophthalmological Society in 1887. But the hint then given has not received the attention this matter deserves. It is the lens I use most constantly and would find most inconvenience from losing, of any in my

trial set; and my assistants and students have come, by working with it, to place the same estimate on its value. It can, of course, be imitated by taking a convex and a concave cylinder from the trial case, placing them with their axes perpendicular and using in the manner to be presently indicated; but a combination that is used so constantly, in every case, whether hyperopic, myopic, or astigmatic, it is much better to have constantly at hand ready for use.

When we have placed before the eye a sphero-cylindrical combination of lenses, supposed to be approximately the correction, and wish to test it by varying its strength, it is perfectly easy to alter the strength of the spherical without in any way effecting the cylindrical factor of the combination. When, however, we attempt to change the strength of the cylinder by holding before it the proper convex and concave cylinders from the trial set, we at the same time alter the general convex and concave effect of the lens. And so, without the corresponding change in the spherical, we do not get simply a change of cylindrical effect, but a double alteration that may be very misleading.

This can best be illustrated by taking a special case. Suppose the combination hit upon to be a +2. spherical with a +0.50 D. cylinder, while the glass really required is a +1.5 D. spherical ⌒ +1. D. cylindrical. The holding of a convex 0.5 D. cylinder in front of the first combination, would be certain to make the vision worse. And although just that additional strength is needed for the cylindrical, the natural inference from such a trial would be that it was not needed. The same difficulty about fixing the strength of the cylinder will be experienced so long as the proper strength of spherical has not been exactly obtained. And each error of the kind into which the surgeon is led entails a considerable loss of time in finding out it is an error and correcting it.

Of course, by using in every case both a convex and a concave cylinder and turning them each, first, to correspond with the axis of the cylinder already before the eye and then perpendicularly to it, such errors may be avoided. But besides the additional time this requires, the transition from the lens which improves the vision to the lens, which most markedly impairs it, requires a complete change of the glasses held before the eye, as well as a change of their direction, and the lost time, diminishes the force of the contrast between improvement and impairment, by which, the patient has to judge.

The use of the lens is simply, as has been indicated by the foregoing remarks, to hold in front of the approximate correction already placed before the eye and by alternately placing it so that it will first increase and then diminish the strength of the cylinder in the combination already fixed upon, to ascertain whether the cylindrical factor is of exactly the best strength.

The writer, instead of the actual crossed cylinder, has always employed the sphero-cylindrical equivalent with a concave spherical, and a convex cylindrical side. In this case, the axis of the cylinder marked on the glass corresponds with the axis of the convex cylinder that is increased by it, or is at right angles to the axis of the concave cylinder that it adds to.

The strengths found most generally useful in practice are the concave 0.50

D. spherical combined with the convex 1. D. cylindrical; the concave 0.25 D. spherical combined with the convex 0.5 D. cylindrical; and the concave 0.125 D. spherical combined with the convex 0.25 D. cylindrical. Of these three, the second is the most generally used. It is, however, best to have all of them and begin by using the strongest, unless vision equal to very nearly the full normal standard has been obtained by the combination first tried. Then, as the correction is made more and more accurate, the weaker lenses are to be employed in the same way.

Commonly, it is best to ascertain first that the strength of the spherical cannot be improved by any change; and then to use the crossed cylinder to fix the strength of the cylinder. But where the cylindrical portion of the lens is very strong, it may be better to reverse the order. First to ascertain, by turning slightly either way, where the cylinder in front of the eye gives the best vision, and then to use the crossed cylinder to correct its strength, before doing anything with the spherical part of the combination.

This matter may seem to be one of minute detail and small importance, but I have not known any one who had carefully tried it, who would be willing to work without the aid of such a lens, or who regarded it as a matter of little importance. This is its value even where the refraction of the eye is entirely constant under the influence of the mydriatic, but if one wishes to determine the strength of cylinder required without the use of the mydriatic, the crossed cylinder—indicating whether the cylinder supposed to be the proper one should be strengthened or weakened entirely independent of the accomodation of the eye, or at least of the regular accommodation of the eye—is quite invaluable.

Comment: Jackson's most important contribution to refraction was the perfection of the cross-cylinder. In the above article he proposed the cross-cylinder test for determining the precise amount of astigmatic error. In 1907 he announced the even more valuable cross-cylinder test for astigmatic axis, an application that was entirely original. Jackson's cross-cylinder was used quite differently from that first described by Stokes in 1849. Stokes noted that two cylinders of equal but opposite power neutralize each other when their axes are parallel; but if one cylinder is gradually rotated from this position, an astigmatic lens is formed of a power varying continuously from zero to twice the astigmatic power of either lens. After the cylinder is thus turned until it best suits the eye, a reference to a table gives the refractionist the information regarding the power of the indicated cylinder. The Stokes lens could only give an approximate measurement of well-marked astigmatic errors upon the basis of an axis previously established by other means as by the distortion noted in viewing a distant small circular light. The Stokes lens, as well as its later modification by Dennett, remained but a scientific curio except for its adaptation by Jackson as a malingering test. For this purpose Jackson placed in the trial frame a pair of 2.0 D. cylinders of opposite power with axes vertical over the admittedly good eye. Then while the subject, with both eyes open, viewed the chart, the outer cylinder was rapidly flipped 90 degrees. This created a lens equal to $+2.00\ S/-4.00\ C \times 180$ that reduced the vision of the good eye to less than 20/200, so that whatever was read registered the acuity of the other eye.

Jackson stressed that the cross-cylinder should be rotated while the subject was observing the smallest letters discernible through the instrument. The 0.25 D. cross cyl-

inder is generally used, but the 0.12 D. or 0.50 D. cross-cylinder may be more useful when the acuity is above or below average respectively. In aphakia, some use the 1.00 D. cross-cylinder. Though letters or figures are the usual test object, the accuracy of the test may be affected by the psychologic phenonomenon that the distortion in which the vertical components are clear is preferred over the reverse. This difficulty is overcome by the concentric circles introduced by Verhoeff, now available in the Projectochart and in transilluminated near-vision slides. The examiner need but ask whether the circles are more perfectly round in the first or second position of the cross-cylinder. A highly accurate refinement in the determination of axis is the Crisp-Stine test, used with the simple cross-dial in which the midpoint of one of the four arcs is marked by the apex of a small triangle. After the preliminary refraction, the eye is fogged 0.25 D. and both the trial cylinder and the triangular marker are placed at the presumed axis. The 0.12 D. cross-cylinder is applied, and the query is whether the cross-lines look more alike before or after the turn of the cross-cylinder. If the presumed axis was correct, the application of the cross-cylinder shows a contrast in the lines that is reversed on rotation of the instrument; if incorrect, the axis of the trial cylinder is shifted towards that position of the cross-cylinder which makes the lines look more alike. With both the trial cylinder and the triangular marker at the same axis, the tests are repeated until the axis is precisely localized.

The cross-cylinder is absolutely indispensable to those familiar with its use. Nevertheless, the instrument is still but little known outside the United States.

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BIOGRAPHICAL NOTE

Edward Jackson (1856–1942) was born in Chester County, Pennsylvania of Quaker ancestry, though he later became a Unitarian. After graduation as civil engineer, he embarked on the study of medicine and received his medical degree from the University of Pennsylvania in 1878. While engaged in general practice, an attack of diphtheria, subsequently complicated by paralysis of ocular accommodation, shifted his interest to ophthalmology. The background in engineering, as with Javal and Prentice, attracted him to physiologic optics. His writings, which included a book on Skiascopy (1905), contributed greatly to the perfection of refractive technique in America. In 1888 he was appointed Professor of Ophthalmology at the Philadelphia Polyclinic at the age of 32; and in 1890 he became Surgeon at Wills Hospital. The advent of tuberculosis in his wife determined the departure of the Jackson family to Denver in 1894. After her demise two years later Jackson continued in Denver as he feared a predilection of his children to this dread disease.

Jackson was a leading figure in ophthalmologic societies and headed the Section of Ophthalmology, A. M, A., in 1894, the American Academy of Ophthalmology and Otolaryngology in 1903, and the American Ophthalmological Society in 1912. Then, as now the optometrists were battling the medical refractionists, but with more reason. They pointed out that many physicians with little special training were doing refractions under legal sanction. To remedy this situation Jackson conceived a plan of extra-legal certification of ophthalmologists. His suggestions prompted the creation of the first such

certifying agency, the American Board for Ophthalmic Examinations. The idea gradually spread to the other medical and surgical specialties so that a total of 14 examining boards are now functioning. Jackson devoted his life to the education of the American ophthalmologist. He was a founder of the Colorado Ophthalmological Society (1899), Professor of Ophthalmology at the University of Colorado (1905) and initiated in 1923 a two-week postgraduate course that became the prototype of similar enterprises all over the country. When Jackson became editor-in-chief of the present American Journal of Ophthalmology (third series) in 1918, he infused new life in the journal by combining with it the previously published Ophthalmic Record, Annals of Ophthalmology, Ophthalmology, and the Ophthalmic Yearbook and Literature which he had launched in 1904. An endless array of pointed editorials revealed his vast and brilliant erudition. Jackson was awarded the Lucien Howe Medal of the American Ophthalmological Society and was the first recipient of the Leslie Dana Medal for special achievement in the prevention of blindness. The instruction program of the American Academy of Ophthalmology and Otolaryngology was inspired by him. At the 1942 session in his 87th year he gave a course on office management, just 15 days before his death.

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Book Reviews

"Ophthalmologie—Directives therapeutiques médico-chirurgicales," by G. Offret and G. Lombard. *G. Doin et Cie. edit., Paris, 1959. Vol. in 8; 370 pp., ffr. 3.750.*

In the collection of the "Bibliotheque de therapeutique médicale," a volume on the various treatments of ocular disease available to date is presented.

The authors start with a review of all the symptoms observed in ophthalmology stating briefly for each of them their acknowledged pathogenesis and medical as well as surgical treatment.

In a second part the various groups of therapeutic agents used in ophthalmology are studied and their mode of action and application discussed.

In the third part the treatment of ocular diseases is considered according to their anatomical location so that a therapeutic outline is given for each affection within the orbit.

Finally in the last two parts are reviewed the treatment of the infectious processes such as tuberculosis, mycosis, etc. as well as ocular tumors.

The value of the book is mainly in its conciseness, giving in 370 pages a clear synopsis of ophthalmologic therapeutics. The book is schematic and does not consider experimental pharmacodynamics or clinical data to sustain any proposed therapy. It is written for the practitioner, the student and the beginner in ophthalmology to acquaint them with the essentials in ocular therapy. For the ophthalmologist it is a good memento to remind him at a glance of the possible therapeutic approach to any given ocular problem.

An alphabetic index completes the book. There are no illustrations or bibliography.

H. E. Chodos

"Geographic Ophthalmology—Asia, Australia and Africa," edited by William John Holmes, M.D. *Charles C Thomas, Springfield, Ill., U.S.A., $8.50.*

Dr. William Holmes is a well traveled ophthalmologist especially in the areas of Asia, Australia, and Africa. He resides and practices in Hawaii and is well familiar with the common eye diseases found in tropical, subtropical and arid areas of the world. By virtue of his knowledge of the visual suffering in these particular parts of the world, he has attempted, by bringing together the contributions of 20 other world-spread authors, to develop some standardization of procedures and improvement of techniques that might contribute to the restoration of sight and the prevention of blindness.

This text does not attempt to include all the major eye diseases that occur in

Africa, Asia, and Australia and related areas but to give the ocular manifestations of a few systemic diseases and the medical and surgical treatment of a few eye diseases of regional importance. Notable among these are leprosy which is discussed by Dr. William Holmes, onchocerciasis which is presented by F. H. Budden of Northern Nigeria, Africa, and trachoma which is carefully considered by Mahmud Ali Shah, Dr. Tulsi Das, Dr. M. S. Nirankari, Dr. M. R. Chaddah and Dr. Geminiano de Ocampo. Dr. Shah is Professor and Head of the Department of Ophthalmology at Dow Medical College, Karachi, Pakistan. Dr. de Ocampo holds a similar position at the University of the Philippines, Manila. Dr. Chaddah is from the Department of Ophthalmology, Medical College of Amritsar, India.

Dr. V. K. Chitnise of Bombay has tackled the colossal problems of blindness in India. The estimated incidence of blindness in the State of Bombay is approximately 516 blind persons per 100,000 population. With the exception of Egypt, the incidence of blindness in India is higher than elsewhere in the world. This chapter clearly presents, through the written word and the associated photographs, a brief description of the major visual problems still to be conquered in India.

Dr. Alvaro for years, until his untimely death, had been campaigning for all ophthalmologists in the world to pool their ideas and technical knowledge in an effort to spread this information beyond national boundaries, to those many countries throughout the free world where organized ophthalmology practically does not exist. He suggests many ways in which improvements can be brought about through organization.

Dr. Guha of India has considered many of the ocular complications of malaria and presents an interesting patient with sympathetic ophthalmia who appeared to improve following the exacerbation of malarial infection. He comments on some of the complications of drug therapy such as the optic atrophy and visual field impairment associated with quinine, the blurring of vision due to large doses of chloroquin and the yellow discoloration associated with the use of mepacrine.

Corneal ulcers are commonly encountered in this area of the world, and therapy is outlined for this condition by Agarwal, Lecturer in Ophthalmology at the Medical College of Agra, India. He stresses the importance of vitamins in the therapy, such as vitamin A, vitamin C and also nicotinic acid.

Keratomalacia, a preventable disease, is an economic and social problem for its proper control is related to the diet. This disease is rare in Europe and America but relatively common in China, Japan, and India. Eight per cent of the blindness of Calcutta and Madras is estimated as being caused by keratomalacia.

An intriguing chapter on westernizing of the oriental eye is presented by Bergis T. Saack of Quezon City, Philippines.

Various surgical procedures for correction of pterygium and for the irradiation of pterygium are also considered and Sato, Head of the Department of Ophthalmology, Juntendo University School, Tokyo, Japan, has presented much of his own surgical techniques for the correction of corneal astigmatism, keratoconus, handling of anterior and posterior synechia, after cataracts and pupillary mem-

branes. It is doubtful if very many surgeons in this country would be willing to undertake this technique for the correction of refractive errors and Sato, himself, feels that his technique of surgical treatment of myopia still leaves a great deal to be desired.

The problems of cataract surgery have universal appeal, and in this text there is a chapter on cataract surgery as an office procedure and the details of the Smith-Indian technique of extraction.

Other subjects covered include solar corneal-retinal burns and a rather detailed discussion of ocular rodent ulcers by Peter English of Brisbane, Australia.

It is quite obvious in perusing this text that there is a great deal for ophthalmology to offer to the remote and distant patient of its already acquired knowledge. There is the problem of getting the information and therapy to the patient who needs it. The ophthalmologists working in Europe and the Americas must appreciate the tremendous efforts and tasks well performed by their colleagues working in the tropical, subtropical, and arid areas of the world.

IRVING H. LEOPOLD

"Transactions of the Ophthalmological Society of the United Kingdom, Volume LXXVIII (78)." *J. & A. Churchill, Ltd., 104 Gloucester Place, Portman Square, 1958, about $18.00.*

The present volume comprises the Proceedings of the Ophthalmological Society of United Kingdom during its 78th session held in April, 1958, together with reports of the Proceedings of the Affiliated Societies of 1957 and 1958. These transactions, as usual, are well written and provide pleasurable and informative reading. The scope of the subjects included is extremely broad. Several papers deal with the complications of hypermature cataracts that can be avoided by early surgery. Considerable attention is given to the production of phacoanaphylactic and phacotoxic uveitis as well as to the means of differentiating between the closed angle glaucoma and that due to an intumescent cataract.

Among the discussions dealing with lens are those on the role of ectodermal development of crystal lens, correction of uniocular aphakia, evaluation of anterior chamber acrylic implants and other types of lenticular implants and the problem of binocular vision in cataractous patients.

Glaucoma has received considerable attention in the various society meetings. Stress is placed on the importance of paying attention to minute details in the operative procedure one follows in doing filtration operations in an effort to prevent conjunctival fibrosis. The incidence of primary glaucomas and the priscol test as well as the role of tonography in the early diagnosis is covered. As in previous issues, the management of idiopathic primary glacuoma, of provocative tests and the methods of early clinical diagnosis of the disease are informatively discussed.

There are a number of presentations concerning uveitis, its etiology and therapy. The importance of toxoplasmosis was considered but no decision reached as to its relative importance as an etiologic factor in uveitis.

A thorough discussion of topical antibiotics and chemotherapeutic agents in

ophthalmology by Ridley is of considerable practical value. Dr. Ridley feels that normal tears are an effective barrier against infection by a wide range of pathogenic bacteria.

Dr. Townley Payton reviewed the complications of keratoplasty and stressed the value of β-irradiation for the prevention of vascularization of the graft. He believes this is the greatest single threat to a clear graft. Irradiation should be applied before surgery in order not to interfere with healing. Dr. Payton stressed the value of preliminary lamellographs especially if they are made slightly larger than a projected penetrating graft. The remnant scar tissue around the periphery is likely to inhibit vascularization during the postoperative period. Dr. Payton is in favor of the clover leaf or figure 8 suture with the stitches crossed in the center of the graft. Effort should be made to see that the stitches are evenly placed and the pressure distributed equally over the entire surface of the graft.

A rather delightful discussion of the cataract section has been made by a group of individuals including John MacLean, Harold Ridley, J. L. E. Werner, F. A. Williamson Noble and others. The argument still goes on concerning the value of the Graefe knife versus the keratome for the initial section.

In another section, the indications for clinical electroretinography are discussed by Karpe and is worth perusing.

There is a very rewarding discussion of cancerous and precancerous melanosis of the conjunctiva and it is apparent that there is still much confusion with regard to the nature of the disease and its relation to similar lesions elsewhere.

Consideration of the not too unusual condition of rhabdomyosarcoma of the orbit was considered and early exenteration recommended. It was suggested that irradiation be held in reserve for any recurrence.

A study of the 1958 Transactions would be rewarding to any ophthalmologist although he might be quite frightened by the pictures of the patient with anorexia nervosa who developed cataracts, particularly if he were indulging or contemplating dietary limitations for himself.

IRVING H. LEOPOLD

Refresher Lectures

CURRENT METHODS OF CORNEAL PRESERVATION

J. Harry King, Jr., M.D.*

The innumerable research reports published in recent ophthalmic literature indicate that there is a definite need for a satisfactory method of preserving donor corneas for keratoplasty. Efforts to solve this problem have been stimulated by the fact that corneas are not readily available for the increased demands occasioned by progress in corneal surgery. It therefore seems opportune to summarize present day knowledge of the various methods of corneal preservation and their application to modern ophthalmic surgery.

LAMELLAR KERATOPLASTY

The revival and development of better techniques of lamellar corneal grafting have greatly expanded the field of keratoplasty. Its indications include a wide variety of applications directed toward increasing vision, improving the anatomic and physiologic status of the cornea, and as a treatment for corneal disease. Therapeutic lamellar keratoplasty offers the widest field of application in corneal surgery. The increased incidence of recurrent or chronic neurotropic or viral keratitis, for which there is no adequate medical therapy, makes the demand for corneas urgent. A lamellar graft will prevent blindness when it is used as an emergency procedure for a ruptured corneal ulcer, a descemetocele, and for certain eye injuries.

When benefit can be expected, lamellar keratoplasty rather than penetrating grafting should be used because it entails less risk for the patient. The demands for donor corneas for the lamellar operation far outweigh the needs for material for penetrating keratoplasty.

Methods of Preservation

Three methods for the preservation and storage of corneas for prolonged periods are currently in use—freezing, lyophilization (freeze-drying), and glycerine-dehydration. The results obtained with the use of lamellar grafts

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preserved by these methods have proved as successful as those obtained with fresh donor corneas. For certain types of therapeutic grafting, these preserved grafts may actually be preferred to fresh tissue because of their reduced antigenic properties.

1. Freezing. Many investigators have attempted to preserve animal corneas by rapid freezing. Smelser and Ozanics[1] reported failure in penetrating transplantation with corneas which had been frozen. Polge, Smith, and Parkes[2] broke the preservation barrier in 1949 by the accidental discovery that the pretreatment of certain tissues with glycerine-saline solution before freezing resulted in cellular survival. It is now well established that the protecting properties of glycerine are necessary in the freezing of animal tissues.

In 1954, in England, Eastcott and his co-workers[3] reported success in the preservation and transplantation of frozen human corneas. Full thickness and lamellar cadaver corneas were placed in small sterile bottles and covered with 15 per cent glycerine in Ringer's solution (pH 6.0). After standing at room temperature for 1 hour, the solution was decanted leaving only enough to barely cover the grafts. Tight screw-topped stoppers were used to close the bottles which were then immersed for several minutes in a mixture of carbon dioxide and alcohol slush at −79°C. The bottles were stored in a dry container with solid carbon dioxide (Dry-Ice) held in a special box (Perspex) at −79°C. This container was then placed within a standard commercial deep freeze. When the cornea was needed for grafting, it was thawed by immersing the bottle in a water bath at 40°C. and the glycerine solution was replaced by fresh Ringer's solution. Immediately before the cornea was to be used for corneal grafting in the operating room, it was transferred to normal saline solution containing 1000 units of penicillin per milliliter. The lamellar and full thickness grafts, after thawing, seemed normal in every way.

Five lamellar grafts which had been stored from 3 days to 9 months were used and the results were successful in all instances. The postoperative course was the same as for fresh corneas. Seven full thickness grafts were performed with grafts which had been stored from 5 days to 7 months. They were considered successful in 2 patients and partially successful in 3. Clearing of the graft occurred much later in the postoperative course, however, than would have been expected if fresh grafts had been used.

It was concluded by these investigators that lamellar grafts can be stored indefinitely by this method and that these grafts will give results equal to those obtained with fresh corneal material. The routine use of frozen full thickness grafts was not advocated, since it was felt that further study was necessary to solve the reasons for failure.

Ryeroft[4] has had extensive clinical experience utilizing corneas preserved by this method. Regarding full thickness grafts he states "we have proved that a clear graft can be obtained after six months preservation, but we have not the desired consistency in the results."

Stocker and his co-workers[5] have examined the viability of the three corneal layers—epithelium, stroma, and endothelium—separately in tissue culture.

Positive cultures from corneas frozen at −79°C. were obtained only from the epithelium and stroma. All cultures of the endothelial layer were negative and no positive cultures were obtained from any layer after 4 weeks of storage in the frozen state. They concluded that the endothelium is not viable at any time after treatment by the method outlined, and that the stroma and epithelium are viable for only a limited period.

2. Lyophilization (Freeze Drying). Bonhoure[6] in 1955 reported the successful use of a cornea preserved by lyophilization for lamellar keratoplasty in a patient with a recurrent pterygium. In 1958, in France, Payrau and his associates[7] published extensive studies on the utilization of corneas preserved by lyophilization. They stated that lamellar homografts compared favorably with those done with fresh graft material, but that penetrating homografts were successful only in exceptional cases. Enucleated cadaver eyes were stored in Dry-Ice until they were prepared for lyophilization. At this time, a segment 1 cm. in diameter was excised from the posterior pole of the eye and the contents of the eyeball were aseptically removed. The cornea and sclera were placed on special supporting trays which stretched the sclera so that its original shape was maintained. The globes were quickly immersed in a mixture of 90 per cent alcohol and Dry-Ice and left for 5 minutes. They were then placed in jars which had been previously reduced to the same temperature and which had the opening protected by a filter. The jars were put in a desiccation tank where the temperature was maintained for several hours at −50°C. A vacuum of 10^{-3} mm. Hg completed the desiccation. Gradual reheating of the jars was carefully observed in relation to the established vacuum, and a temperature of −40°C. was reached when desiccation was complete. This required about 12 hours, although the apparatus was allowed to run for 18 to 20 hours. The jars containing the eyes were then sealed hermetically in a nitrogen atmosphere rarified with the aid of a vacuum pump and stored at room temperature without any special precautions. At the time of rehydration, the jar was filled with physiologic saline which had been kept at a temperature of +35°C. The globes gradually resumed their normal consistency and the corneas regained transparency. One to one and one half hours was required to rehydrate the human eye. According to these investigators the eye was thoroughly rinsed in physiologic serum in order to remove certain antigenic substances liberated by the lyophilization process.

The lyophilized grafts had been stored from 1 to 7 months. Oxygen consumption studies and tissue cultures proved that lyophilized corneas were not viable. Studies of the antigenic properties indicated a reduction of the antigenicity factors by the lyophilization technique.

These investigators also reported good results with the use of lyophilized lamellar *heterografts* when the species of the donor was properly chosen. Heterografts from dog to man did well, but similar grafts from pig to man did very poorly. They felt that the use of a lyophilized dog cornea was an excellent therapeutic procedure in lamellar grafting for corneal herpes, since the dog cornea is naturally refractive to herpes. Penetrating heterografts with any species always resulted in failure and the procedure was not performed on human beings.

In these studies it was indicated that lyophilization resulted in total desiccation of the corneal tissue. After rehydration, the dried cornea recovered a nearly normal physical and histologic structure. For animal eyes, the loss of moisture content, or loss of weight at the end of the lyophilizing procedure, was from 75.5 per cent to 76 per cent. After rehydration, the graft gained 114 per cent of its original weight, indicating that it absorbs very little water.

In 1959, Payrau and Pouliquen[8] published a preliminary report which simplified the desiccation of the cornea by the use of chemicals. The excised cornea was quickly frozen in a mixture of ethyl alcohol and Dry-Ice slush for a period of 15 to 20 minutes. The tissue was then rapidly dried, wrapped in cellophane, and plunged into a flask containing a small quantity of microporous silica gel. The flask was hermetically sealed and a vacuum was obtained by means of a tube from the flask placed in water. As it was desiccated, the frozen cornea became transparent and dried to a horny consistency. When the cornea was needed for use, the tissue, with its cellophane wrapping, was plunged into warm physiologic saline to rehydrate for 8 to 10 minutes. The cornea became soft and resumed its normal thickness and transparency. Payrau and Pouliquen reported further that a simpler modification to the desiccation technique omitted freezing the tissue before chemical drying. The cornea was wrapped in cellophane and placed in a flask containing the silica gel. The flask was hermetically sealed in a vacuum. They stated that this method did not guarantee the sterility of the graft and that the graft was more difficult to cut than from the corneas which had been dried by the first method. After rehydration, the corneal tissue had a gelatinous consistency. Although transparent grafts were obtained with four human lamellar keratoplasties, these investigators felt that further histologic and biologic studies were needed before the method could be properly evaluated.

3. Glycerine-Dehydration. In 1953, McNair[9] experimented with the lyophilization of animal corneas and concluded that this technique left the cornea with no cohesive structure to maintain its form and that the process was too destructive to the corneal tissues. With the knowledge established by others[2, 3] that pretreatment of tissues with glycerine-saline before freezing protected the tissues from the detrimental effects of freezing, McNair conceived the idea of combining dehydration with the use of glycerine.

In 1955, McNair and King[10] published the results of animal experiments in which corneas preserved by dehydration in glycerine were used. Entire corneas were removed from cats and placed in a glass container with a solution of 15 per cent glycerine and isotonic saline. The bottle was then cooled by immersion in a mixture of crushed solid carbon dioxide (Dry-Ice) and alcohol. The container was connected to the manifold of a dehydrating system with a vacuum pump modified from that used to lyophilize arteries. After all the water was removed and dehydration was complete, the corneas were stored in air-tight containers at room temperature. Corneas which had been stored for as long as four months were rehydrated and yielded clear lamellar grafts. Penetrating transplantation was not attempted in these experiments.

King,[11] in 1956, reported on a modification of the previously mentioned experiments in which corneas were dehydrated in 95 per cent commercial glycerine and the tubes sealed in a vacuum and stored at room temperature. Nine animal corneas, stored for a maximum period of seven months, and five human corneas, the oldest having been preserved for almost two months, were used successfully for lamellar grafts. Penetrating grafts were not transparent in animals and they were not evaluated in human beings.

The results of further studies on preserving corneas by dehydration in glycerine were published by King[12] in 1958. In this method, the cornea was excised together with a 4-mm. rim of adjoining sclera. It was placed in a sterile Pyrex test tube containing 5 cc. of 95 per cent glycerine and 30 minims of antibiotic mixture. The tube was not immersed in a mixture of Dry-Ice-alcohol slush but was connected directly to the glass manifold of the closed dehydration system. When dehydration was complete, the tube was hermetically sealed with a gas-oxygen torch and was stored in a vacuum at room temperature.

Corneas preserved in this manner were used for lamellar grafting in over 50 patients, and the results were considered equal to those obtained with fresh material. The oldest corneas had been stored at room temperature for 2 years. King stated that when lamellar keratoplasty was required for therapeutic purposes in certain types of keratitis, a preserved cornea appeared to be preferable to a fresh one. There was less postoperative inflammation of the eye and more rapid clearing of the cornea. This was thought to indicate less antigen-antibody reaction, possibly because some of the tissue proteins had been removed during the dehydration process. The clearing effect on the surrounding diseased cornea appeared greater and there was less vascularization of the preserved graft. He felt that the therapeutic effect of the graft might have been enhanced by the use of the antibiotic mixture as a rehydrating medium. Penetrating grafts with tissues preserved by this method were not adequately studied.

In a further elaboration upon the use of corneas preserved by dehydration in glycerine, King and Chavan[13] reported that several surgeons, after brief observations, had successfully used these corneas in penetrating keratoplasty. They concluded, however, that although the use of these corneas for lamellar grafting could be advocated with impunity, there was not sufficient evidence available at that time to recommend their use in penetrating transplantation unless an emergency measure was required to save an eye. At the present time, limited studies have shown that corneas preserved by this method do not remain clear after penetrating grafting.

PENETRATING KERATOPLASTY

There is no satisfactory method at present for the long-term preservation of donor corneas for penetrating corneal transplantation. Occasional clear penetrating grafts have followed the use of corneas preserved by each of the three methods just described as being uniformly successful for lamellar grafting. The inconsistency of results, however, does not justify their elective use for penetrating keratoplasty. If an emergency measure is required to save an eye, a

preserved graft can be used and can be expected to heal normally although the endothelial layer may become opaque.

Methods of Preservation

1. Moist Vapor Chamber. In the United States, this method is the one commonly used for storage of fresh donor eyes. The eye is kept in moist air in a sterile glass container fitted with a ground glass stopper or a tightly screwed top. The eye rests on a cotton dental roll saturated with aqueous Merthiolate or is held suspended by a metal frame over cotton soaked with normal saline solution. The container is stored on the bottom shelf of a refrigerator (4°–6°C.).

Authorities disagree on the maximum storage time allowed by this method. Paton[14] stated that the experience of the New York Eye Bank indicated that an adult eye enucleated immediately after death may be kept in good condition for as long as 3 days. Stocker[15] felt that transplantation should be performed within 24 hours after the eye had been removed from the donor. He noted that endothelial changes occurred if they were held in cold storage for longer periods.

2. Liquid Paraffin. In England, the method of Carrel adapted to cornea preservation by Burki[16] is generally used. Enucleated eyes are placed in liquid paraffin with a mixture of streptomycin and penicillin. The container is refrigerated at 4°C. until the eye is needed. Rycroft[17] obtained successful penetrating grafts from eyes preserved for as long as 3 weeks by this method.

DISCUSSION

It can be assumed that donor corneas do not have to be viable to give clear results for lamellar transplantation. Oxygen consumption studies and tissue cultures by many authorities[5, 7, 18, 19] have proved the nonviability of corneas preserved by freezing, lyophilization, and dehydration in glycerine. A viable and functioning endothelium seems to be a prerequisite for a successful penetrating graft.[5]

Stocker *et al.*[5] stated that it is possible that improved preserved tissue might even be preferable to fresh tissue. There is no doubt that this is true when preserved corneas are used for therapeutic lamellar grafting in human beings. Payrau and associates[7] noted reduction of the antigenicity factor by lyophilization, and King[20] felt that the antigenic properties of corneas preserved by dehydration in glycerine were minimized.

CONCLUSIONS

Corneas can be preserved for long-term storage for successful use in lamellar keratoplasty. The methods of (1) freezing after pretreatment with glycerine and storage in the frozen state, (2) freeze-drying (lyophilization) and storage sealed in vacuum at room temperature, and (3) by dehydration in concentrated glycerine and storage in vacuum at room temperature, are all equally useful. We prefer the glycerine dehydration method, because of its simplicity, ease of storage and shipping, and because it does not distort or wrinkle the cornea tissue.

Long-term storage of corneas for penetrating keratoplasty have met almost complete failure. It is hoped, however, that in the near future current research studies may lead to the development of a successful technique. The discovery will not be a revolutionary one but will probably evolve from one of the methods currently successful for lamellar grafts. It is possible that the endothelium will survive if freezing is slow and thawing is rapid. Newer developments in cell survival by rapid freeze-drying may be applied to corneal preservation.

The preservation methods now in use are a notable advance. They have solved the problem of supplying donor material for lamellar grafting when fresh tissues are not available. In modern surgery, the demands for corneas for lamellar keratoplasty far outweigh those needed for penetrating grafting. The general population is not yet educated in the donation of eyes and therefore eyes must be conserved. A satisfactory means of avoiding waste and offering a more constant supply of donor corneas can be accomplished by:

1. Making fresh corneal material which has been stored no longer than 24 hours at 4° to 6°C. available for penetrating keratoplasty only.
2. Utilizing for lamellar grafting eyes which have been stored in a moist chamber from 24 to 72 hours.
3. Establishing several preservation units in centralized eye banks where corneas could be preserved for long-term storage. These should include eyes not requested after 72 hours and "weekend" donor eyes which are not needed for grafting in a particular area at that time.

Preserved corneas could then be held in reserve by eye banks or hospitals and would be made available to any eye surgeon for immediate use as an "eye-saving" measure, in an emergency, or for routine lamellar keratoplasty. A penetrating graft is always an elective procedure and can await the procurement of a fresh donor eye.

SUMMARY

The current methods of corneal preservation have been reviewed. Several techniques are useful for the long-term preservation of corneas for lamellar grafting. At present, fresh corneas offer the best material for penetrating keratoplasty. An eye bank procedure is recommended for conserving corneal tissue, which is now in short supply. Wastage would be prevented and corneas would be more readily available to all eye surgeons.

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A CONSIDERATION OF MULTIPLE FACTORS IN THE ETIOLOGY OF UVEITIS

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The first factor to be considered in any disease state is, naturally, the etiologic agent. Over the years we have accumulated quite a list of agents that are known or suspected to cause uveitis. Even when we consider granulomatous and nongranulomatous uveitis separately, it is still a nonspecifically caused disease; that is, many agents cause the clinical picture of uveitis. It is the purpose of this paper to investigate the avenues to specificity—to suggest a way of finding what single factor or factors are constant and invariable in clinically diagnosed uveitis.

An inflammatory disease can be broken down into two interreacting components: an agent and a host. Nearly a century ago, Pasteur finally conceded to Claude Bernard that the germ was less important than the "soil" into which it fell. True, there are some agents, *Bacillus pyocyaneus* for instance, that are so virulent that hardly any "soil" can contain them without being destroyed. But

we are not referring to these agents because they would soon overwhelm the eye and completely destroy it. On the contrary, most agents involve a rather selective portion of one eye and may then cease their activity.

Many workers in different branches of medicine have considered the "soil" in which an agent will produce an effect. It will have to suffice for our purposes to say that some soils defend themselves better than others against inflammatory agents. Selye further differentiates between internal responses which stimulate defense and those which inhibit defense. But the end result is what counts. Either the cells within a tissue will break down or change their function or both, or else they will not be affected. We now come to a consideration of what factors (other than the agent itself) will determine whether the tissue will or will not respond to the agent.

As we pursue the mainstream of our knowledge, it is at this point that it divides into two tiny rivulets. They have been discovered and named by many explorers, but few have been privileged to follow. So little is known that we might as well name them ourselves and refer to *individual vulnerability* and *tissue vulnerability*. Under the former would come all of the factors that make this person an inflammation-susceptible individual. One might suspect that a patient with a high circulating adrenocorticosteroid level would, at that time, be practically inflammation-proof; however, most of us are not. We are likely to get coryza, laryngitis, pleuritis, enteritis, and rheumatism whenever the weather changes for the worse. Others are even less fortunate. Early in life they start having dermatitis and later progress to hives, hay fever, and asthma. We are not at this time asking whether it is the same etiologic agent that causes all his allergies, but rather, what it is about him that makes him respond with so many inflammations.

Let us consider several suggestions that have already been offered about individual vulnerability. Rich states that there are inheritable individual differences in the ability to make antibodies. Zweifach discovered that by temporarily bleeding a dog he can make the animal 1000 times more sensitive to bacterial endotoxins than it was previously. He believes that the reticuloendothelial system may become depressed, and in consequence of this blockade, as it is called, there is an exaggerated response to bacterial products. Epstein finds, on questioning patients who had a flare-up of uveitis, that many had had "an influenza-like episode," which is necessary to set the stage for an attack of uveitis. It was postulated that this intercurrent "clinical event" might be either physical or psychic.

Schlaegel has recently suggested that there are psychologic factors in uveal inflammation. In a preliminary survey of uveitis patients, he found that a significant proportion of uveitis patients suffer from mental disorder. If this is the case, then it remains for us to investigate the exact nature of the mental disorder; that is, whether this is a disorder of mood, of ideation, or of adjustment to significant persons and events in the environment. If we can answer these and other questions about the mental life of our patients, we may learn some specific facts about the individuals who are vulnerable to ocular inflammation.

If our knowledge of individual vulnerability is markedly lacking, our knowl-

edge of tissue or organ vulnerability is practically nonexistent. Under consideration here is the question of why one particular organ or system collapses rather than another, when the same stress is applied to all. More specific to our problem is the question why, of all the vascular tissues in the body, should an inflammation be localized to a tiny, circumscribed area like the uvea. Several suggestions have been offered. For granulomatous uveitis, it may be that organisms localize or metastasize to an area of damaged tissue. For nongranulomatous uveitis, it may be that the eye becomes traumatized (emotionally traumatized or sensitized?) while a certain antigen is circulating in the blood, and the uvea henceforth responds to that same antigen with inflammation. Along another line, Waksman noted that even in the presence of hypersensitivity, lesions may not develop unless there is some alteration of the blood-tissue barrier. What causes these local alterations in the blood-tissue barrier remains an open question. The question, I feel, remains open even though such agents as histamine and adrenaline should be implicated because there would still be no known reason for the abnormal accumulation in the eye.

To explain ocular vulnerability, the psychologic approach may yet prove the most fruitful. We know already from psychiatry that the mind may regard the parts of the body in different and special ways. Because psychiatrists have studied hysteria, we know how the unconscious mind of a professional pianist feels about his hand when he develops a hysterical paralysis the night before an important concert. Similarly, we have no trouble accepting the intervention of the mind in hysterical amaurosis. Because in both cases the inhibition takes place on the highest cortical levels and does not directly involve the effector organ, we can say, "It's all in the head." But skepticism enters when there is a visible, organic lesion in the tissues. It would be tempting to review all we know about the neural and humoral connections between eye and brain, but such is not the purpose of this paper. Here we are concerned with the highest cortical mechanism and the final uveal response.

In uveitis patients who have lost considerable function, we have an opportunity to learn the meaning of the eye, albeit with reference to loss or injury to the organ. There are different levels of the unconscious, some being much nearer to consciousness. At one unconscious level the eye has one meaning, while at another level it may have an entirely different significance. Probably the eye is one thing to the hysterical amblyope and quite another to the uveitis patient. The hysteric merely shuts off his vision, while at the other extreme the psychotic may actually remove the eye. If we do not know why an eye should offend him "if thine eye thee. . ." then how can we say why he should pluck it out? More generally, if we cannot say what the eye means to a patient, how can we say what will happen to it.

THERAPEUTIC IMPLICATIONS

Apart from therapy directed specifically against the agents of uveitis (antibiotics and adjuvants), our most common and potent remedies are directed to the individual or host. These treatments are nonspecific and are as diverse as fever therapy to cause stress and rest to reduce stress. Yet somehow they all seem

to be effective in rendering the patient less susceptible or less responsive to the agent of inflammation. Possibly the inflammation in the eye is not of sufficient extent to elicit an alarm reaction with subsequent adaptation. In this case, fever therapy would initiate a therapeutically adequate response. Corticosterone is, of course, one of the products of this response, and its use is of inestimable value in uveitis. There is a splendid rationale for use of a therapy that will stop a useless and harmful inflammatory response on the part of the body, but we have still not reached the *cause* of the disease. When corticoids are stopped, there is always the danger of recurrence; when they are indefinitely continued, there may be undesirable consequences from the profound physiologic alterations.

Various authors have commented on the nonspecific value of hospitalization for some uveitis patients. It would be an advantage to know which ones will not remit without it. Further, it would be helpful to know what, precisely, is the therapeutic action of hospitalization. Are we satisfying dependency needs which the individual cannot ask for directly, or are we merely removing him from the presence of an irritating member of his family? Finally, are there some cases that for some reason react adversely to hospitalization or to removal from the stressful situation?

If we knew the answers to these questions, we would be able to change nonspecific therapy into specific remedies. For example, if we detected a universal depression, we might use the newer psychic energizers. If the common factor was invariably an irritating member of the family, some strong advice might be in order. But before any remedy could be routinely applied, we should know what is common to all uveitis patients, besides the inflammation. If there is any factor shared by all, then, except for untreatable constitutional factors, we should find an appropriate therapy.

Treatment for the organ vulnerability is at present limited to cortisone and atropine, applied locally. It would be very nice if the area of inflammation could be shifted for a few centimeters, let us say into the nose. This is perhaps not so ridiculous a hope. Under hypnosis, erythema and urticaria have been made to appear in one location and then in another, on command of the hypnotist. In the course of psychoanalysis, inflammation in one organ or system may be exchanged for a lesion in another. There is undoubtedly both reason and order in these shifts, as well as in the original site of the lesion. From long and careful interviews with people, we learn that many persons are very sensitive about some organs. A lesion or operation on this organ upsets the mind, and, conversely, a disturbance in the mind may be reflected in disturbed physiology in this organ. Thus, the eye can be one such "target organ"—as the psychiatrists call a *locus minoris resistentiae*. In order to prevent repeated attacks, the pathologic connection between the mind and its target organ must be exposed and dissolved. Somewhat as the surgeon, by vagotomy and sympathectomy, severs a connection between brain and effector organ, so must the psychiatrist do by psychologic means. In this way, he should be able to prevent these antigen-antibody wars from taking place on a battleground in the uvea.

Special Article

CATARACT FORMATION IN HUMAN AND EXPERIMENTAL DIABETES

PART II

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PATHOGENESIS OF DIABETIC CATARACT IN MAN

The review of the experimental work concerning alloxan and galactose cataract presented, can leave no doubt as to the importance of the energy supplied through carbohydrate metabolism in maintaining lens transparency. Protein turnover must go on continuously and the electrolyte and water balance must be maintained. Various means of producing cataracts would seem to take the common route of deranged carbohydrate metabolism, sapping the lens of its vital power.

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There are still many difficult problems awaiting solution such as the exact role played by insulin in the carbohydrate metabolism of the lens. Insulin if it is to reach the lens in any quantity must penetrate the blood aqueous barrier into the anterior chamber. The variations of sugar in the blood, and its relationship to the sugar content of the aqueous humor must also be considered. The lens epithelium is a most fascinating structure as it is responsible for producing the majority of high energy phosphate compounds required by the lens. How does it react to various stimuli, such as insulin deficiency or excess glucose in the aqueous humor? These are but a few of the many questions concerning the lens and carbohydrate metabolism in diabetes. The relationship of carbohydrate metabolism, if any, to the important problem of cataract formation of the senile type must also be taken into consideration. The answer to most of these questions will have to await further research.

The lens acquires most of its metabolic requirements such as glucose, oxygen, amino acids, etc. from the aqueous humor and disposes of waste products such as lactic acid and CO_2 by the same means. In order for substances to reach the aqueous, they must traverse the blood-aqueous barrier.

As long ago as 1914, Ask remarked that a rise in blood sugar resulted in an increase of the sugar content of the aqueous humor within an hour. The same author (1927) found the ratio of blood sugar to that of aqueous to be 1.2:1, whereas the sugar content of the vitreous body is lower than that of the aqueous. Adler (1930) agreed with Ask in noting that in every instance where blood and aqueous were drawn at the same time, sugar levels were higher in the blood. Furthermore, diffusion from the anterior to the posterior chamber took place very slowly, if at all, at normal intraocular pressures, the iris-lens contact forming a water tight barrier to the passage of fluid from the anterior into the posterior chamber. The aqueous promptly follows the rise and fall of blood sugar, whereas the vitreous shows a definite lag in equilibrating its sugar level. Adler suggested that this phenomenon could help explain the transitory refractive change noted in diabetics, but did not explain changes in astigmatism.

Glucose, galactose, methyl glucose, and xylose all penetrate into the aqueous humor at about the same rate, whereas sucrose penetrates much more slowly (Davson and Duke-Elder, 1948). The following electrolytes and nonelectrolytes were found to penetrate into the aqueous humor in decreasing order as follows: CNS^-, Na^+ and K^+; monosaccharides; glycine, alanine and creatinine, urea, sucrose and phosphate (Davson *et al.*, 1949). Blood galactose penetrates rapidly into the aqueous humor, reaching a concentration of about 75 per cent of the plasma: the concentration of glucose in the anterior chamber is 0.8 that of plasma (Harris and Gehrsitz, 1949). The low limit of molecular size which can pass into the aqueous humor is exemplified by the fact that the aqueous humor is almost protein free. Ross (1951) demonstrated that the rate of penetration of various nonelectrolytes into the aqueous humor depended more upon their lipoid solubility than on molecular size or chemical structure. In the case of the sugars, the hexoses, glucose and galactose, and the pentose xylose, are anomalous in that they are highly lipoid insoluble and yet they exhibit penetration rates

which are far in excess of other substances of that order of lipoid solubility, *e.g.* sucrose.

Ross found that substances of a high relative lipoid solubility had high permeability constants. In 1952 the author showed that by inducing diabetes in rabbits with alloxan, the rate of penetration of glucose into the anterior chamber was profoundly reduced, to about 50 per cent that in the normal rabbit eye. Insulin, on the other hand, increased the rate of penetration. The author in a later study (1955) showed that anterior pituitary growth-hormone had a similar effect.

The rate of glucose uptake by isolated, decapsulated rabbit lenses was accelerated 350 per cent by insulin. When homogenates of lens were used, the rate of glucose uptake by insulin was augmented by only 33 per cent. These experimental facts led Ross (1953) to conclude that insulin mediates an enzymatic transport mechanism and in its absence glucose must enter by solution in the cell membrane or by passage through pores. Low lipoid solubility and high molecular weight of sugars would slow down their rate of traversal immensely. The hyperglycemia of diabetes may apparently result from the inability of glucose to enter the cells, rather than a failure of intracellular enzymatic oxidations.

Insulin has been shown to accelerate the transport of both glucose and galactose into muscle fibers *in vivo* (Levine *et al.*, 1950). In diabetic rats insulin prevents cataract formation and restores the normal growth curve (Patterson, 1953*a* and *b*). Lowering the blood sugar by phloridzin also delays or prevents cataract formation, even though the other symptoms are aggravated. In a review of experimental diabetic cataracts (1956), Patterson pointed out that a minimum time is required for the maturation of a cataract, regardless of the level of the blood sugar. The author was of the opinion that in the absence of insulin, the uptake of glucose by the lens is impaired and the total available energy is lowered beyond the critical point for maintenance of transparency. A special fructose-high fat diet can be utilized in absence of insulin to provide energy, thereby preventing development of cataract in spite of hyperglycemia.

Studies of the accumulation and utilization of glucose within the rabbit lens treated with various enzyme inhibitors have indicated that glucose does not enter the lens solely by simple diffusion, but by some active process involving metabolic mediation (Harris *et al.*, 1955). In this study, the role of insulin in the transport of glucose across the lens barrier was not established, but the authors felt that this barrier lies in close proximity to the lens capsule.

Dische *et al.*, (1953) suggested that the lens capsule was not a passive structure but regulated permeability actively, since they found glutathione and nucleotides in the capsule separated from epithelium, with very little of these substances in the aqueous humor. Pare (1954) maintained that the lens capsule, epithelium and superficial stroma function as a membrane with selective permeability and that most cataracts are caused by permeability changes. The author included diabetic cataracts as one of a group resulting from permeability disturbances. Von Sallmann and Locke (1951) could find no alterations in the

uptake of P^{32} by the irradiated lens *in vivo* until the lens was practically opaque. These experiments did not lend any support to the theory that changes in capsular permeability or a diminution of phosphorylation processes cause opacification of the lens, but suggested that they are secondary to the original pathologic alterations.

It is generally accepted that an elevated blood sugar of a certain duration will result in cataract formation in the experimental animal (Rodriguez, 1954; Charalampous and Hegsted, 1950). Embryos of rats fed galactose during pregnancy are born with lens changes (Bannon and Kaan, 1939). Babel (1954) described cataractous changes in a 14-week-old fetus of a severely diabetic mother. Hyperglycemia in humans may result in lens opacification and the form taken is dependent upon the severity of the disease and the age of the patient. However, there is little agreement as to the role played by minor alterations in carbohydrate metabolism such as slight elevations in fasting blood sugars or abnormal glucose tolerance curves in the older age groups presenting with senile cataracts.

In 1922 Löffler found a higher fasting blood sugar as well as a prolonged glucose tolerance curve in older individuals. In a study of the sugar tolerance in aglycosuric cataract patients, Langdon (1922) noted 13 out of 17 with abnormal glucose tolerance curves. In another group of patients, the same author (1925) examined 100 patients with senile cataract and found 15 per cent with abnormal blood sugars, whereas 45 per cent were unable to "digest a glucose meal normally." Different authors have confirmed this impression (Malkin and Krassikov, 1927; O'Brien, 1928 and 1932; Galindez, 1929; Mehlhose, 1929; Palmerini, 1931; Bellows, 1944; Schlossman, 1956).

Lottrup-Andersen (1923) reported the sudden postinfluenzal appearance of cataract in a 58-year-old woman, with only a previously diminished sugar tolerance. Shastid (1929) was surprised to note the disappearance of lens opacities with the onset of a severe diabetes in one of his patients. However, this seemingly remarkable exception does not disprove in any way the relationship of hyperglycemia and cataract.

Cataract is known to mature more quickly in the diabetic than in the nondiabetic (Scott, 1953).

The glucose content of normal lens is 60 mg. per 100 gm. of fresh tissue, whereas that of the senile cataract is 46.3 mg. per 100 gm. as opposed to 82 mg. per 100 gm. in the diabetic cataract (Lottrup-Andersen, 1927).

In 1929 the same author wrote that the glucose tolerance curve in the cataractous patient is not significantly different from that in the noncataractous patient of the same age group. The phosphorous content of the senile cataract in the diabetic was found to be low in comparison to that found in the ordinary senile cataract. Diabetic patients are no more likely to have cataracts than nondiabetic patients, according to Waite and Beetham (1935). However, this statement cannot be considered exact as far as the juvenile diabetic is concerned, nor does it disprove the fact that the incidence of abnormal glucose tolerance curves in cataractous patients is unusually high. The same authors observed 297 diabetics under the age of 20 and found 11 or nearly 4 per cent with diabetic cataracts.

All of these patients with lenticular changes were severe diabetics requiring large doses of insulin, and approximately one half of the cataract patients were poorly controlled at the time of their first examination. In the remainder the typical opacities appeared and multiplied in spite of the most satisfactory control of the diabetes. Dehydration is considered one of the factors in the pathogenesis of the lens changes observed in the acute form of diabetes (Lawrence *et al.*, 1942).

The interesting studies of Harris and Gehrsitz (1951) concerning changes in the potassium and sodium content of the lens emphasized the importance of various metabolic processes maintaining a normal cation distribution. A failure of this control mechanism leads to lenticular intumescence. As is well known, most living cells exhibit a higher potassium and lower sodium than is found in the extracellular fluid. This is due to active transport and not impermeability of the cell membranes. The authors point out that the lens has a higher potassium and lower sodium than is found in the intraocular fluids, and a normal exchange goes on continuously. In cataract production, a decrease in potassium and increase in sodium content of the lens occurs tending towards equilibration with extralenticular fluid.

An important feature of cation shift is the likelihood that it provides a mechanism for intumescence of the lens. The cell membrane can become fully permeable to cations in the absence of a compensatory secreting mechanism, the cell tending to swell and rupture under the influence of the osmotic pressure. Harris and Gehrsitz found that if glucose is replaced in the medium of a lens culture *in vitro*, by xylose, fructose or galactose, a moderate but still quite extensive redistribution of sodium and potassium as well as an uptake of water by the lens will occur. Thus, we can readily see that any alteration or change in the normal metabolism of glucose will have an immediate effect on the electrolytic and water balance of the lens. Bonavolonta (1950) demonstrated a diminished glucose metabolism in animal lenses made cataractous by massage. He found the glucose content of the aqueous in these animals to be abnormally high, whereas the lactic acid content was low.

The diminished glutathione (GSH) content of the lens has been demonstrated in cataract formation (Cohen *et al.*, 1928; von Euler and Martius, 1933). Glutathione and vitamin C are both synthesized by the lens. Their exact function is still speculative but they are believed to participate in the oxidation-reduction system of the lens. The diminished glutathione content of the lens is the earliest biochemical change taking place before visible opacities. Bellows and Shoch (1950) demonstrated that the glutathione content of the lens after alloxan injection first occurs after 3 days and only after the blood sugar level has started to rise. The authors suggested that the decrease in GSH is part of the initial cataract formation and is not an effect of the alloxan itself. A well known phenomenon is the immediate disappearance of reduced glutathione from the blood upon injection of alloxan. It is therefore presumed that alloxan does not have a direct effect on the lens, especially since the diminution of GSH occurred only in the animals subsequently developing diabetes.

A reduction in glutathione content of the lens cortex in the galactose-fed rat

occurs before the appearance of any visible opacities (Rosner *et al.*, 1938). The changes in ascorbic acid were much more variable, as were glutathione changes in the lens nucleus.

The exact relationship between reduced glutathione and cataract formation on the one hand, and reduced glutathione and diabetes on the other hand, is difficult to establish at the present time. A state of metabolism similar to that observed in clinical diabetes mellitus can be produced in normal men and women by the administration of suitable amounts of a purified preparation of pituitary adrenocorticotrophic hormone (Conn *et al.*, 1949). Sustained glycosuria, hyperglycemia and glucose tolerance curves characteristic of the diabetic state as well as a relative resistance to the hypoglycemic effect of exogenous insulin is noted in these subjects. Accompanying features observed were a drop of the blood glutathione, as well as a temporary upheaval of purine metabolism resulting in an increased excretion of uric acid in the urine. The authors believed that the purine metabolite exerting an alloxan-like effect is responsible for reducing the intracellular availability of free SH, impairing functional activity of the insulin producing cells of the pancreas and also interfering with peripheral glucose utilization by inhibition of those enzymes requiring free SH. The injection of GSH had an immediate but transitory effect lasting 1 to 2 hours. The effect of GSH in simultaneously reversing ACTH induced hyperglycemia and renal glycosuria seems all the more striking since sudden cessation of glycosuria would be expected to result in further increase of hyperglycemia were the rate of utilization of glucose not significantly increased or the supply to the blood significantly decreased. Not all of the metabolic effects of increased adrenal corticoid activity were reversed by the administration of GSH. This indicates that reversal of those metabolic effects which responded to GSH was not by virtue of a block in steroid production. Conn *et al.* conclude that the changes are due to improved performance of those systems which require free sulfhydryl groups for their normal function.

It is interesting to note that the reduced glutathione content of the red blood corpuscles seems to be slightly but definitely increased under the influence of insulin (Zunz, 1931).

Glutathione is not found in the aqueous humor (Carteni, 1937; Herrmann and Moses, 1945). The amino acid content of normal aqueous humor is considerably lower than that of the blood plasma (Wunderly and Cagianut, 1954). The glutathione content of lens cortex varies from 388 to 570 mg. per 100 gm. and that of the nucleus from 64 to 100 mg. per 100 gm. (Herrmann and Moses, 1945). Kinoshita and Merola (1958) confirmed the distribution of glutathione in the lens. Kinsey and Merriam (1950) demonstrated a decrease of 40 per cent in reduced glutathione (GSH) content in the lenses of rabbits fed 2 to 4 gm. of naphthalene daily for about 5 days, though no opacities were visible. The authors also showed with the use of labeled glycine that the glutathione in the lens is undergoing a continuous turnover disposing of the question as to where the lens obtains glutathione. Glutathione is synthesized from its constituent amino acids at a rate of about 2.5 per cent per hour. Kinoshita and Masurat (1957)

studied the possible relationship between glutathione and carbohydrate metabolism. Their results suggested a possible interaction of the dehydrogenases of the shunt mechanism and glutathione reductase. Even though the lens possesses a high peptidase activity it does not have the ability to hydrolyze glutathione very rapidly. From 80 to 90 per cent of the glutathione in the lens is in the reduced form, and oxidized glutathione is converted to the reduced form by normal lens extract (Sato, 1956). Daisley (1955) pointed out that the irradiation of lenses resulted in a loss of their ability to synthesize GSH. The author did not feel that the destruction of glutathione-synthesizing enzymes of the lens was a primary effect of irradiation, but that progressive loss of this synthetic ability does result and may well be closely associated with the course of lens opacification.

However, if glutathione is administered to animals before irradiation, the incidence of conspicuous sutures in the lenses of animals exposed to x-irradiation is decreased. Glutathione administration protected glucose 6-phosphate dehydrogenase, and no decrease in cytochrome oxidase activity in the lens followed x-irradiation (Swanson *et al.*, 1957). Von Sallmann *et al.* (1950) noted the protective action of cysteine against x-ray damage to the eye. In using a single dose of 1500 r, epilation of the lids and development of lenticular opacities were influenced beneficially when cysteine was injected intravenously before irradiation, but not when the amino acid was administered shortly after the exposure.

Vitamin C synthesis from hexoses occurs in the normal lens, whereas this does not take place in experimental traumatic cataractous lenses (Ogino and Sasamoto, 1951*a* and *b*). The amount of vitamin C in the aqueous humor depends on the presence of vitamin C in the lens (Bietti, 1935). In naphthalinized animals a reduction of aqueous vitamin C in proportion to opacity formation is observed. Bietti related a similar situation in cataractous patients. Hawley and Pearson (1938) noted decreased vitamin C content of the cataractous lens from 30 mg. to 10 mg. per 100 gm. of lens tissue and also a diminished excretion of vitamin C in the urine of these patients. The authors found no correlation between age and vitamin C content of the lens, but a dietary history showed diminished uptake of foods rich in vitamin C in the older age group and low income. However, Bietti points out that the lens is producing less vitamin C resulting in a decrease in the aqueous humor, but that the lowering of the vitamin C is not the cause of the cataracts.

The enzyme, glutathione reductase in the lens, as demonstrated by van Heyningen and Pirie in 1953, implements the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH) in the presence of reduced triphosphopyridine nucleotide (TPNH) which is oxidized to TPN. The possible importance of this reaction was emphasized by Kinoshita (1955) who found that the citric acid cycle was relatively inactive in the lens, and his results led him to believe that the aerobic phase of glucose metabolism is different in the lens than in other tissues. The experimental results indicate that in the lens, the direct oxidative pathway or hexose monophosphate shunt accounts for most of the CO_2 produced from glucose. It seems that for every four molecules of glucose utilized by glycolysis, one molecule of glucose is shunted through the direct oxidative route.

In the two-step oxidation of glucose-6-phosphate in the hexose monophosphate shunt two enzymes are involved, glucose-6-phosphate and 6-phosphogluconic acid dehydrogenase. Both of these dehydrogenases require the presence of TPN as their coenzyme and in this process TPN is reduced to TPNH. Therefore, the possibility of reoxidizing this enzyme must exist in the lens. TPNH can be oxidized by the chain of respiratory enzymes involving the flavoproteins and cytochromes, or in the reaction involving glutathione reductase of van Heyningen and Pirie. However, some means must exist whereby GSH is oxidized in order that the circle of reactions be closed. Dische and collaborators (1953) demonstrated that lens capsule is capable of oxidizing glutathione. Pirie and van Heyningen (1954) found that under certain circumstances lens extract is able to oxidize GSH by dehydroascorbic acid.

Thus, we can gain some insight as to the possible functions of glutathione and ascorbic acid in lens metabolism. Kinoshita (1957) is of the opinion that since the lens is essentially acellular with the cytochrome system confined almost entirely to the mitochondria, the reoxidation of TPNH by the cytochrome system would be sluggish. At their very best, experiments *in vitro* are subject to great caution in interpretation. We can safely conclude that these various systems are present in the lens, but the relative importance of each still requires further research.

The anomalies observed in glutathione and vitamin C content of the lens during cataract formation, induces speculation as to the role of these substances in the metabolic picture of the physiologic and pathologic lens. It is our opinion that cataract formation follows a common pathway beginning with deranged carbohydrate metabolism. The metabolic alterations manifest themselves differently depending upon the lens terrain, but the biochemical alterations have strange similarities in the various types of cataracts. These findings in experimental diabetic cataracts are similar to those found in cataracts induced by many varied means, such as x-rays, or naphthalene.

The relationship of insulin to cataract formation in the diabetic state is of great interest. There are many instances on record relating the reversal of lens opacities with amelioration of the diabetes after insulin treatment. Refractive changes occurring at the same time are probably all linked to one basic process. Michail and Vancea (1927) did not observe opacification of the lens in the naphthalinized rabbit if insulin was administered. The authors invoked a lesion of the pancreas as being normally responsible for the cataract. From 2½ to 3 hours after the subcutaneous injection of insulin, the sugar content of the aqueous humor is decreased to 63 per cent of its normal level, whereas that of the blood is lowered 53 per cent, vitreous 37.5 per cent and cerebrospinal fluid 57 per cent (Nakayasu, 1934). However, the subconjunctival injection of long acting insulin did not moderate the development of cataract in alloxan-diabetic rats (Barany and Brolin, 1954).

It is only in recent years that the complete amino acid sequence of insulin has been elucidated (Ryle *et al.*, 1955). There has also been some confusion as to the molecular weight of insulin. Harfenist and Craig (1952) supplied data

giving support to the concept of insulin having a molecular weight of approximately 6500. However, insulin contains 1 mole of Zn per 12,000 molecular weight (Tanford and Epstein, 1954). The molecular size of insulin is of importance to us, as it determines to a certain degree the permeability of the protein across the blood-aqueous barrier. A direct effect on the lens can only be possible if insulin penetrates into the aqueous humor. On the other hand, insulin may regulate the permeability of the blood-aqueous barrier to various nonelectrolyte substances.

The presence of I^{131}-labeled insulin in the aqueous humor after intravenous injection in the rabbit has been investigated. In an earlier paper, Giles *et al.*, (1958) found the concentration of I^{131}-labeled insulin in the aqueous to be 0.1 that of the plasma, after intravenous injection of 50 μc. per kg. in the rabbit. The trichloracetic acid precipitable activity in the aqueous reached a maximum within an hour after injection. The data of Scott *et al.* (1958) did not support the assumption that the trichloracetic acid precipitate of radioactive insulin in serum represents only intact, biologically active insulin. However, the authors found that the use of electrophoresis to separate I^{131} insulin from plasma appears to be accurate as compared with the biological assay method using the rat diaphragm. Giles and Harris (1958) obtained similar patterns of radioelectrophoretograms from the aqueous and plasma of normal, diabetic and hyperglycemic normal rabbits.

However, only a small fraction of the activity measured in the plasma which could be considered as biologically active insulin was found in the aqueous humor. The authors concluded that insulin does not enter the aqueous in physiologically significant concentrations and that so far as insulin availability is a measure, the lens is always in a diabetic state. More research will have to be done concerning the penetration of insulin into the aqueous humor and its mode of action as concerns the lens. The concentration of insulin in the aqueous humor of the anterior chamber may not be the same as that in the posterior chamber. Therefore, the presence of even small quantities of active insulin in the anterior chamber can take on quite a different aspect. The aqueous humor of the posterior chamber is possibly depleted of insulin as it comes in contact with the lens epithelium. The action of insulin on the lens is perhaps localized entirely to the lens epithelium. We will expose our reasons for entertaining this hypothesis.

Insulin has been the subject of many investigations ever since its discovery by Banting and Best in 1922. In a recent review, Stadie (1957) gave an excellent summary of the current ideas concerning the action of insulin. Studies with I^{131}-labeled insulin have shown different binding capacities of the different tissues. Muscle and liver bind large amounts of insulin compared to other tissues, whereas the brain has never been shown to react to insulin and contains no bound insulin following intravenous injection of the hormone. The binding capacities of the structural elements of the liver, that is, the mitochondria, nuclear fraction and microsomes are different, indicating a specificity of the binding. In the rat diaphragm *in vitro*, response to bound insulin diminished in the alloxanized animal. Cortisone and growth hormone had similar effects, whereas hypophysectomy rendered the animals extremely insulin sensitive.

So far as muscle is concerned, it is now generally held that impairment of the hexokinase reaction does not play any role in the decreased ability of this tissue to metabolize glucose. Park *et al.* (1955) and Park and Johnson (1955) demonstrated with rat diaphragm, heart or skeletal muscle that the metabolic block in the absence of insulin is concerned with an inhibition of glucose transport across the cell boundary. Levine and Goldstein (1955) as a result of their experimental work concluded that in the absence of insulin, galactose is practically excluded from the muscle cell. This step antecedes and is distinct from glucose phosphorylation by the hexokinase reaction.

However, there is evidence that this is not the case in the liver, and that the metabolic block in glucose utilization by hepatic tissue is probably a block in the hexokinase reaction. The diabetic liver also shows a decreased ability to synthesize fatty acids.

Bertolini and Barozzi (1954) demonstrated that glucose-1-phosphate disappears much more rapidly from the blood of diabetics than from normal subjects. This again indicates that one of the defects of metabolism in the diabetic may be the original phosphorylation process.

The oxidation of certain metabolites by the Krebs' cycle brings about the incorporation of inorganic phosphate into energy-rich types of organic combination such as adenosine triphosphate. These reactions are collectively grouped under the term oxidative phosphorylation, and probably occur almost exclusively in the mitochondria. Vester (1957) in Stadie's laboratory demonstrated that the isolated mitochondria of liver cells from depancreatized cats showed defective oxidative phosphorylation activity which could be reversed by prior treatment of the diabetic cats with insulin. Stadie concludes that oxidative phosphorylation is definitely impaired in the diabetic state and that this impairment cannot be ignored as a possible factor for departures of both fat and carbohydrate metabolism from normal.

We have seen from the work of Kinsey and Merriam on the lens epithelium, that most, if not all, of the high energy compounds are formed at this level. It seems logical by analogy to attribute to the mitochondria of the lens epithelium the major role in the formation of the high energy phosphate compounds such as adenosine triphosphate. Decreased oxidative phosphorylation activity of the mitochondria in the lens epithelial cells in the diabetic state is a most attractive theory but must await experimental confirmation. Furthermore, if the administration of insulin could be shown to exert an influence on the mitochondria of the lens epithelial cells, we would have the long awaited explanation as to cataract formation and its reversal in diabetes by insulin administration.

Giles and Harris (1957) were unable to demonstrate that insulin has any effect on the movement of glucose across the lens surfaces or on the utilization of glucose by the isolated intact lens. Ross (1953) found that the utilization of glucose by decapsulated lenses was markedly increased in the presence of insulin, but Giles and Harris could not confirm this with C^{14}-labeled glucose in the presence of HGF-free crystalline insulin in either the normal or alloxan diabetic animal. Farkas and Patterson (1957) found the glucose uptake of the lens significantly reduced after destruction of the insulin-producing cells by alloxan.

However, the uptake was significantly increased after injection of insulin in the rat before death. Insulin added to the incubation medium did not alter the glucose uptake of isolated lenses. This suggested to the authors that the insulin effect was mediated through some other organ. The concept was supported by the fact that complete evisceration abolished the insulin effect, whereas evisceration with retention of the liver conserved the effect on the lens.

Renold *et al.* (1955) were unable to establish a consistent, reproducible effect of insulin *in vitro* with liver slices. The intravenous administration of 5 to 10 units of insulin 10 to 70 minutes before sacrificing the animal did not affect the rate of hepatic glucose phosphorylation, even though the dose was sufficient to give a drop in blood glucose from 447 mg. per 100 ml. to 231 mg. per 100 ml. No early insulin effects on hepatic carbohydrate metabolism could be demonstrated, whereas the effect of insulin on diaphragm was apparent within minutes after the intravenous injection. Treatment for two weeks with small doses of insulin was required in order to restore normal metabolic function of the intact alloxan diabetic rat as well as its liver and diaphragm (Spiro and Hastings, 1958).

Alterations in carbohydrate metabolism has attracted attention as a possible explanation in the pathogenesis of senile cataract, but no conclusive experimental work in this direction has as yet been produced. It is interesting to note that oxidative phosphorylation with β-hydroxybutyrate as the substrate declined in liver mitochondria from aged rats (Weinbach and Garbus, 1959). However, similar decrements were not seen with the use of other substrates. Brain mitochondria did not show any age associated declines in oxidative phosphorylation with succinate as substrate. We may recall that the brain apparently does not utilize insulin for its carbohydrate metabolism.

Results obtained from studies on labeled amino acid incorporation into mitochondria, both *in vivo* and with the isolated particles, show that mitochondria are able to incorporate amino acids into protein (McLean *et al.*, 1958). Isolated liver mitochondria can catalyze the incorporation of amino acids into protein at an appreciable rate and this process is adenosine triphosphate dependent. Bates *et al.* (1958) have presented evidence suggesting the incorporation of labeled amino acids into cytochrome *c*, but the immediate role of ATP in the process is not known, that is, the possibility that energy is needed only for amino acid transport into mitochondria, has not been excluded.

The link between carbohydrate and protein metabolism is ever becoming clearer in the light of these recent investigations. Analogies should and even must be made between the metabolism of the lens and the other tissues. Their verification will certainly bring solutions to many difficult problems.

The relationship of oxidative phosphorylation to senile cataract as well as to diabetic cataract is of the highest interest and investigations of this nature are being undertaken at this laboratory.

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Clinical Practice

THERAPEUTICS

STEROID THERAPY IN SKIN DISORDERS

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J.A.M.A., 1959, *170:* 1311–1315

One of the most useful agents introduced for topical dermatologic therapy in the past 20 years has been hydrocortisone (Cortef, Cortril, Hycortole, Hydrocortone) and some of its derivatives. It is the purpose of this paper to review and condense the results of the more exhaustive studies on the use of steroids in skin diseases.

The vast majority of patients with skin diseases use the steroids in topical preparations. Used in this way, there are rarely any systemic side-effects, and the patient requires far less supervision than when the steroids are given orally. As with any other disease for which steroids are used, skin diseases are controlled but not cured by these compounds. It is extremely difficult to adequately control the vast majority of skin diseases with steroids alone; it is still necessary to obtain a detailed history, perform extensive diagnostic procedures, and make a proper diagnosis before any attempt to use steroids can be considered. The introduction of steroids to dermatology has complicated rather than simplified the management of dermatoses.

Many skin diseases, particularly the eczematous group, will respond to systemic or topical administration. Other skin diseases, such as those associated with systemic collagen diseases, pemphigus vulgaris, sarcoidosis, drug eruptions, and urticaria, may respond to systemic steroid therapy but not to topical therapy.

Early studies suggested that steroids were not absorbed through the skin or at least did not provoke any physiologic evidence of their absorption. However, it was soon clearly shown that fludrocortisone was absorbed through the skin in sufficient concentrations to give such systemic side-effects as depression of circulating eosinophils, urinary 17-ketosteroids, and urinary sodium, as well as induction of edema and weight gain. Later on tracer techniques revealed that hydrocortisone and cortisone were absorbed through normal skin and that, quantitatively, about 1 per cent of the applied steroid was absorbed and ex-

creted in the urine. Damaging the skin by removing its superficial barrier will allow up to 75 per cent of the steroid to pass through the skin, that is, percutaneous absorption will depend on the extent of cutaneous damage. This explains the wide variation in response of given skin diseases.

Water-insoluble steroids, when injected into human skin, remain *in situ* for extended periods of time and cause characteristic histologic changes in the areas of injection. Water-soluble steroids have little, if any, clinical effect when injected intradermally.

The attached table summarizes many reports in an attempt to determine

Uses of Adrenal Steroids in Skin Diseases

Disease	Route of Administration		
	Oral	Intracutaneous	Topical
	Response*		
Alopecia areata	Good	Good	None
Anogenital pruritus	Good	Good	Good
Atopic dermatitis	Good	Good	Good
Chondrodermatitis nodularis chronica helicis	—	Good	None
Contact dermatitis	Good	Good	?
Dermatitis herpetiformis	Good	—	None
Dermatomyositis	?	—	None
Drug eruptions	Good	—	None
Erythema multiforme	Good	—	None
Granuloma annulare	—	Good	None
Kaposi's sarcoma	None	—	—
Lichen planus	?	Good	None
Lichen vidal	?	Good	?
Localized myxedema	—	Good	None
Lupus erythematosus	Good	Good	None
Lymphomas	Good	Good	None
Mycosis fungoides	Good	Good	None
Necrobiosis lipoidica diabeticorum	—	Good	None
Nummular eczema	Good	Good	Good
Pemphigoid	Good	—	None
Pemphigus vulgaris	Good	—	None
Periarteritis nodosa	Good	—	None
Pityriasis lichenoides et varioliformis acuta	Good	—	None
Postherpetic neuralgia	?	—	None
Psoriasis	?	Good	None
Pustular bacterid	—	—	None
Pyoderma gangrenosum	?	—	None
Sarcoidosis	Good	Good	None
Scleroderma	?	—	None
Solar urticaria	None	—	None
Synovial cysts	—	Good	None
Urticaria	Good	—	None
Xanthoma	—	Good	None

* — = Insufficient data; ? = variable response.

what diseases are improved by the use of steroids and in what form (oral, intracutaneous, topical) they are used to best advantage. Most skin lesions that respond to topical application of steroids will also respond to oral or intracutaneous injection of the steroid. The concentration needed locally, if attained by systemic administration, will usually lead to severe systemic complications if continued over a prolonged period. Intracutaneous use has led to practically no systemic complications, but it may lead to local atrophy or even sensitization by an ingredient in the suspension other than the steroid. These complications are, however, reversible.

Mild systemic side-effects are possible from the topical use of fludrocortisone. Systemic effects from topical use of hydrocortisone or prednisolone, even over large areas for long periods of time, are practically nonexistent. The danger of local infection in areas treated topically with steroids is minimal, except for herpes simplex. Secondary infection induced by steroid therapy has been rare. In general, the higher the concentration of the steroid at its application site the more beneficial it will be. It might be added that cortisone is useless when applied topically.

Comment: It is apparent, after review of Dr. Stoughton's article, that many of the observations in the therapy of skin conditions are similar to those which have been made in dealing with external ocular disorders; favorable responses in the eczematous group to topical or systemic therapy and the occasional favorable response of systemic collagen diseases to systemic therapy but not to local therapy, pemphigus vulgaris, sarcoid and urticaria, also do better on systemic therapy from the dermatologic and ophthalmologic viewpoint. Herpes simplex spreads alarmingly in the skin when treated with steroid therapy. However, secondary infection following local therapy of the skin is rare. It would seem that the higher the concentration of steroid obtained at the local site in dealing with skin afflictions, the more beneficial the effect but, as seen in ophthalmology, very little difference could be demonstrated between a 1 per cent and a 2.5 per cent concentration of hydrocortisone for the therapy of skin disorders.

IRVING H. LEOPOLD

INTRACRANIAL HEMORRHAGE AS A COMPLICATION OF ANTICOAGULANT THERAPY

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Neurology, 1959, *9:* 447–455

Evidence obtained from five cases in which fatal intracranial hemorrhage occurred in patients receiving anticoagulant therapy, together with reports of 58 instances of intracranial hemorrhage during anticoagulant administra-

tion contained in the literature, seems to indicate that the use of anticoagulant drugs is accompanied by an appreciable risk of cerebral hemorrhage in patients with (1) hypertension, and (2) recent cerebral infarction, particularly that due to emboli. Anticoagulant therapy has been advised for patients with the "intermittent insufficiency" syndromes accompanying occlusive disease of the carotid and basilar arteries and recurrent cerebral embolism. Patients with carotid and basilar disease are often hypertensive. The fact that hypertension is frequently associated with spontaneous intracerebral hemorrhage, however, suggests caution in the use of anticoagulants in hypertensive patients. Moreover, cerebral infarcts, particularly those due to emboli and carotid and basilar thrombosis, may be hemorrhagic, with the result that when anticoagulants are administered to a patient with a recent hemorrhagic cerebral infarct, there is a genuine risk of extensive cerebral hemorrhage.

It is not the purpose of this article to deny the value of anticoagulants in treating cerebrovascular disorders. Their value in selected types of cerebrovascular disease has been suggested in various clinical studies. In certain situations, however, cerebral hemorrhage may complicate anticoagulant therapy, often with a fatal result.

Accurate estimation of the frequency and importance of this complication will require further experience with large groups of patients. In the meantime, anticoagulants should be used with caution in patients who are hypertensive or who have recently had strokes.

Comment: Ophthalmologists are frequently called upon to use anticoagulants in the therapy of vascular lesions of the fundus. Although complications are rare, they do occur as demonstrated in this paper. When they do occur, they can be fatal. Considerable caution must be advised in the use of anticoagulants in patients with hypertension or recent cerebral infarcts. There are very few ophthalmic conditions that would justify such a risk.

IRVING H. LEOPOLD

IS THERE A CORTICOSTEROID OF CHOICE FOR RHEUMATOID ARTHRITIS?*

GUEST EDITORIAL

L. EMMERSON WARD, M.D.

J.A.M.A., 1959, *170:* 1318

Currently more than 125 different types of tablets containing an antirheumatic steroid are being sold in the United States. Thus, it is apparent that one of the early problems in the use of cortisone, that of supply, has been solved. How-

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ever, the solution has created a new problem. In this issue of THE JOURNAL (page 1253) Neustadt appropriately calls attention to the doctor's current dilemma, arising from competitive advertising claims and conflicting medical reports, namely, the selection of an antirheumatic steroid for his patient with rheumatoid arthritis.

Seven different cortisone-like drugs, in addition to corticotropin, are now commercially available for, and commonly used in, the steroidal treatment of rheumatoid arthritis. All seven have qualitatively similar antirheumatic effects; however, they differ notably in certain other characteristics.

Cortisone, currently the least costly, has the additional advantage of the longest period of use. Hydrocortisone exhibits antirheumatic and metabolic effects of about the same kind and order as those of cortisone, but is perhaps slightly more potent. Allowing for this small and inconstant difference in potency, there seems to be little or no difference in the systemic effects of these two hormones; equivalent antirheumatic doses produce similar physiologic effects. However, hydrocortisone has proved superior to cortisone in local use, for example, intra-articularly. Hydrocortisone apparently is the chief product of the normal human adrenal cortex; presumably corticotropin exerts its antirheumatic effect chiefly by stimulating the adrenocortical secretion of hydrocortisone.

Prednisone and prednisolone differ structurally from cortisone and hydrocortisone only in the presence of a double bond between the first and second carbon atoms of the steroid molecule. This slight alteration invests these two compounds with an approximately fivefold increase of antirheumatic potency, and unfortunately with a similar increase in the so-called glucocorticoid metabolic activity, when these compounds are compared to cortisone, milligram for milligram. The effect on electrolytes, however, is not increased. Thus, although antirheumatic doses of these compounds equivalent to those of cortisone or hydrocortisone cause less loss of potassium, retention of sodium, and edema, nevertheless they have just as great a tendency to produce the other undesired metabolic effects. The systemic actions of prednisone do not differ significantly from those of prednisolone.

Methylprednisolone seemed to possess a greatly enhanced anti-inflammatory potency and relatively less metabolic activity in animals. When administered to patients who had rheumatoid arthritis, however, it proved to be generally similar to prednisone and prednisolone. Although some investigators have reported that methylprednisolone has a slightly more potent antirheumatic effect than prednisolone and that it produces less edema and fewer of certain other undesired effects, others have found that it has little or no significant advantage over prednisone or prednisolone. Methylprednisolone is neither the first nor the last analogue of cortisone known to affect animals and man differently. Indeed the greater the alteration of the structure from that of the naturally occurring adrenocortical hormones, the greater this disparity generally seems to become. Thus, while investigations on animals provide invaluable screening information, they do not predict accurately the effect of antirheumatic steroids on man.

Triamcinolone also is about equal to prednisone in antirheumatic activity and in most metabolic effects according to many investigators; it is slightly more potent according to others. That it is a significantly better steroid for the treatment of rheumatoid arthritis has not been established, but it does have several noteworthy characteristics. It has little tendency, perhaps the least of currently available antirheumatic steroids, to produce mental stimulation or to cause retention of sodium and edema. Triamcinolone, according to some investigators, causes fewer gastrointestinal symptoms than do other analogues of cortisone. However, peptic ulcers have developed during treatment with this compound; whether it will prove to be less ulcerogenic than its competitors remains to be determined. Triamcinolone causes anorexia and loss of weight in some patients, in contrast to the usually opposite effect of other antirheumatic steroids. An unusual degree of muscular weakness and wasting and erythema of the skin and other vasomotor phenomena have developed occasionally in patients taking triamcinolone.

Dexamethasone, the newest of the analogues of cortisone, is also the most potent, milligram for milligram. Its antirheumatic strength and metabolic effects are approximately seven times those of prednisone. That it has a significant therapeutic advantage over some of its predecessors has not yet been demonstrated. Clinical experience with it, however, is relatively limited and more information is needed concerning results of prolonged usage and concerning certain of its properties such as its effects on the central nervous system, on appetite and weight, on electrolytes, on the formation of edema, on excretion of calcium, and on metabolism of carbohydrates.

Which steroid is best for rheumatoid arthritis? Clinically, some patients seem to fare a little better on one compound, others on another. Certain physicians prefer this steroid, others that. The introduction of each new antirheumatic steroid has been followed by initial enthusiasm during which time the new compound has been hailed by some as showing relatively fewer undesired metabolic effects for a given antirheumatic effect. Experience has shown, however, that considerable time, perhaps several years, is required before the effects of an antirheumatic steroid in the prolonged treatment of a disease such as rheumatoid arthritis can be evaluated properly. And as each new steroid has been used longer and more extensively, its apparent therapeutic efficacy, at least in terms of the more significant metabolic effects, has seemed to approach that of its predecessors. Accurate comparison of the antirheumatic and the metabolic activities of cortisone-like steroids in patients is a difficult, exacting, and time-consuming procedure. Yet many more comparative studies, such as those reported by Neustadt and carried out for even more prolonged periods, are highly desirable.

No one steroid as yet has demonstrated convincing superiority over all its competitors in all, or even in a majority of, patients with rheumatoid arthritis. Generally, the best steroid for treatment of rheumatoid arthritis today is that which is administered by the physician who selects his patient properly, supplements steroidal therapy with other appropriate measures of treatment, supervises the administration of the drug carefully, and regulates the dosage to achieve a

reasonable antirheumatic effect with avoidance of, or a minimum of, undesired effects. Wise usage is of more importance than the particular steroid administered.

Increased potency, in itself, is of no particular practical importance. Of significance, however, is the dissociation of antirheumatic effects from undesired metabolic effects. This has been achieved to a remarkable degree in respect to effects on electrolytes by several of the newer analogues of cortisone, but unfortunately the same has not been accomplished in respect to other metabolic activities which pose much greater problems during prolonged administration. Whether the antirheumatic effect can be dissociated from these other metabolic effects remains to be demonstrated. However, in this age of accomplishment that which seems doubtful or impossible today often will have been achieved by tomorrow.

Pharmaceutical companies at times have been criticized for overenthusiastic advertising of cortisone-like steroids and of other drugs by their sales departments. However, such criticism must be tempered with admiration for the splendid (and costly) achievement in biochemistry, medical research, and pharmaceutical technology which the introduction of a new steroid represents. Likewise, the antirheumatic steroids generally should be blamed less for their imperfections and credited more for their virtues and for the encouragement that even better compounds eventually will be forthcoming.

Comment: In evaluating any new steroid it is important that the agent be tested on the following three groups of patients. (1) It should be tried on individuals who have never been on any other form of steroid therapy to see whether or not the drug is effective here and what the average dose schedule might be. (2) The second group should include individuals who have been tried on other steroids and benefited. They can then be placed on the new steroid, the one to be evaluated, and the results compared as well as the dosage schedule and side effects. (3) The third group should consist of those individuals who have been tried previously on steroids and not responded, then placed on the new steroid.

Only after such studies are we in a position to judge whether the new agent is superior to the old one. All articles which are presented on the use of these agents for ophthalmologic conditions should be reviewed with at least these questions in mind. This editorial written by Dr. L. Emmerson Ward concerning the choice of corticosteroid for rheumatoid arthritis is a good guide for choice of systemically administered steroids for ocular disorders.

IRVING H. LEOPOLD

PERPHENAZINE, A POTENT AND EFFECTIVE ANTIEMETIC*

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J. Pharmacol. & Exper. Therap., 1958, *123:* 306–310

In the past few years a number of phenothiazine compounds have been shown to possess antiemetic properties; among these perphenazine (Trilafon) has been found to be very potent. The present investigation was undertaken: (a) to establish quantitatively the degree of protection afforded by certain doses of perphenazine against relatively large doses of apomorphine; (b) to establish the relative effectiveness of perphenazine and chlorpromazine against apomorphine and other emetic agents, such as morphine, Hydergine and lanatoside C; and (c) to elucidate the mechanism and site of the antiemetic action of perphenazine.

Against emesis induced by 0.1 mg. per kg. of apomorphine hydrochloride, perphenazine was found to be 16.6 times more potent than chlorpromazine. When the doses of apomorphine were increased to 0.5 mg. per kg., the potency ratio was raised to 47.8. Perphenazine appeared to gain in relative efficacy as the emetic stimulus was increased. Perphenazine also was found to be highly effective against vomiting induced by morphine, Hydergine and especially lanatoside C. Therefore, perphenazine was not only a potent, but also a highly versatile antiemetic agent. Whereas chlorpromazine was totally ineffective against emesis induced by digitalis, perphenazine in a dose of 0.1 mg. per kg. prevented vomiting in 67 per cent of such cases. While it is true generally that emesis in digitalis therapy signals an overdosage, nausea and vomiting with doses far below toxicity do occur in occasional patients.

In 1952, Wang and Borison (Gastroenterology, *22:* 1, 1952) reported evidence to indicate the existence of a chemoreceptive emetic trigger zone located in the area postrema, the site of action of many so-called central emetic agents. Animals deprived of the trigger zone bilaterally did not vomit in response to these emetic agents, although their emetic center was intact. The alteration of intragastric copper sulfate threshold under the influence of an antiemetic agent is believed to be crucial in determining whether its site of action is the chemoreceptive emetic trigger zone, the vomiting center, or both. The present experiments indicated that, in dogs receiving threshold doses of intragastric copper, perphenazine in a dose of 0.1 mg. per kg. afforded 27 per cent protection. This fact was interpreted to mean that perphenazine at these dosage levels depressed the medullary emetic center only moderately, and the site of antiemetic action was confined largely to the chemoreceptive emetic trigger zone.

It is therefore suggested that the increased potency and versatility of perphena-

* Reprinted from Survey of Anesthesiology, *3:* 501, 1959.

zine as an antiemetic agent is related to its greater affinity to and its tighter binding with the receptors in the trigger zone.

Comment: This interesting study gives insight into the mode of action of perphenazine. Clinically, this drug is the most useful antiemetic which I have used up to the present. In doses of 5 mg. it is effective in over 95 per cent of patients in the postanesthetic period. It may be given either intramuscularly or intravenously, depending upon the urgency with which relief is required and the severity of symptoms. It is the only phenothiazine derivative which, in effective antiemetic doses, does not cause drowsiness, hypotension, pallor and so on. For this same reason it is equally useful as an antiemetic and sedative in the course of regional anesthesia.

GORDON M. WYANT

SURGERY

FIRST CLINICAL TRIAL AND HISTOLOGIC INVESTIGATION OF FREEZE-DRIED CORNEAL MATERIAL IN KERATOPLASTY

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Acta Ophth., 1959, *37:* 241–252

Living corneal material retaining its structure, such as is obtained from enucleated eyes or from fresh cadavers refrigerated for several days, heals and remains clear in most cases after transplantation. Since fresh cornea is not always available, various methods of preservation have been investigated. It is now clear that corneal material which has lost its structure due to preservation methods cannot be used for grafts. Methods of preservation by either freezing or drying have proved complex and impractical. A method of freeze-drying known as lyophilization, is known to destroy the vitality of the cells but to preserve the corneal structure. The question is whether lyophilized corneas are suitable for grafting. Considerable experimentation has been carried out with variable results, but recent reports by Payrau, Bonel, and Guyard have indicated startling success both in animal grafts and in a series of patients.

A number of methods for lyophilization have been tried, but the best, that of Payrau, seems to be the following: After the eye has been removed, the cornea and part of the sclera are quickly immersed in a mixture of 90 per cent alcohol and carbon dioxide snow at −79°C. for 5 minutes. The drying process is continued in the same medium for 1 hour at −50°C., and for the next 18 to 20 hours is kept below −40°C. in a vacuum of 10^{-3} mm. Hg. The container is then sealed

and placed in a nitrogen atmosphere, and is ready for use. For transplantation the material is rehydrolyzed in physiologic saline under sterile conditions at +35°C. for 60 to 90 minutes. Corneal tissue preserved in this manner is sterile, devitalized, with fully retained physical structure, and it has lost its specific antigenicity so that it may be usable for heterografts.

Results in our first six cases were not successful, and we have sought to explain our failure. First the clinical data should be reported. All donors were men between the ages of 16 and 68. The corneas were removed from 16 to 22 hours after death, and the optical qualities of all corneas were good. The corneas were removed from the globes and frozen in −180°C. liquid air with pentane. The rehydration was done in the same way in all instances, immersion for 30 to 50 minutes in Ringer's solution. The preserved material was used after 5 to 6 weeks. All patients were males between the ages of 3 and 75 years. Three had herpes keratitis, one had a severe burn, and one was a case of amaurosis with beginning phthisis bulbi. All grafts were lamellar, and the diameters of the transplants were 6 to 8 mm. All grafts healed well and were fairly clear for the first week. Vascularization then developed between the host and donor corneas. From the 8th day, swelling began in the stroma of the graft and did not recede. On the 14th day two grafts were removed and successfully replaced with fresh grafts. Three others were retransplanted after 6 weeks. The eye with phthisis bulbi was later enucleated.

The histologic observations of one sample are illustrated in detail. In general, the picture was one of healing difficulty, manifested in the form of massive round-cell infiltration between the host and donor corneas. In tissue cultures the various types of cell growth could not be demonstrated, and histologic examination of similar material confirmed the degeneration of cellular elements.

The explanation of failure in our cases may be that we used an undesirable method of lyophilization, the short period of observation, the severity of the original disease, the relatively large grafts, or the donor material may have been removed too long after death. We are now undertaking further studies using the Payrau method of lyophilization.

Comment: These investigators attempted to preserve corneas by freezing in pentane (isopentane?). The material was stored for 5 to 6 weeks presumably at the same temperature of −180°C. The corneas were used in six patients as lamellar grafts without success. Many past studies have shown that freezing does not preserve corneas for successful penetrating grafting. This work does prove that corneas stored by freezing do not result either in clear lamellar grafts. The method of preservation reported above cannot be properly termed freeze-drying. The tissues were apparently not lyophilized or dried by a vacuum pump or other means. It has been well established that rapid freezing of animal tissues as a method of preservation requires the protecting properties of glycerine. The failures reported by these authors may have been contributed to, as they suggest, by unsuitable donor material as the corneas were removed 16 to 22 hours after death. About 7 hours after death is felt by most authorities to be the maximum time allowable after death for enucleation of "fresh" corneas.

Preserved corneas can be used successfully in lamellar grafting when any one of three

methods of preservation are used: (1) freezing after pretreatment with glycerine and storage in the frozen state, (2) freeze-drying (lyophilization) and storage sealed in vacuum at room temperature, and (3) by dehydration in concentrated glycerine and storage in vacuum at room temperature.

J. H. KING, JR.

THE SURGICAL CORRECTION OF CONVERGENT STRABISMUS (ESOTROPIA)

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Proc. Staff Meet. Mayo Clin., 1958, *33:* 658–663

Opinions differ in regard to the most effective surgical procedure for the correction of convergent strabismus, especially in young children, and also in regard to the most propitious age for satisfactory results. The records of patients with esotropia examined and operated on at the Mayo Clinic from 1950 through 1956 were therefore reviewed and the results evaluated with reference to these points. For the purpose of this report, the term "satisfactory result" is used to indicate a residual deviation of 15 diopters or less; "unsatisfactory result" is used to indicate a residual deviation of more than 15 diopters or exotropia; and "functional improvement" is used to indicate the presence of second or third degree fusion or both after operation, whether it existed before or not. In no instance could third degree fusion be demonstrated preoperatively.

The history in each case revealed some possible precipitating cause of the esotropia in 20 (11.3 per cent) patients. A family history of strabismus was noted in only 33 instances (16 per cent). The refractive errors varied between plus 2.00 and plus 4.00 diopters in the majority of cases. Unusual muscular adhesions and check ligaments reported at operation and the incidence of associated vertical deviations were noted more frequently in patients with greater amounts of esotropia.

Surgical correction was performed in 350 cases during the period under review, but not all of the patients were selected for study. The 176 who were considered suitable for inclusion in this series were those who returned for postoperative tests and who were examined both before and after operation by the same orthoptic technician, with the same type of testing devices. No operation was performed on any patient aged less than 2 years. The period for follow-up studies ranged from 6 months to 6 years.

Conservative methods of treatment were used preoperatively when indicated, except that it was not possible to give orthoptic training in most cases because the patients lived at a distance. The recession-resection operation was used in

the majority of the patients. The data indicate that this procedure produced a substantial number of satisfactory and functional results with minimal undesirable postoperative effects such as overcorrection, incompetence, narrowed palpebral fissures, and the like. The incidence of functional improvement (and satisfactory correction) was highest in patients with less than 40 diopters of deviation, in patients with age of onset of esotropia from 3 through 4 years, in patients having squint of less than 1 year's duration, and in patients having squint from birth to within a range of from 4 to 5 years. The age at which operation was performed did not appreciably affect the end result if considered from this standpoint only.

Comment: The task of analyzing cases of strabismus is so complex that it is not surprising that there is no unanimity about the most effective surgical procedure or the most propitious age for satisfactory results. Not only are there so many variables in cases of strabismus but there is great difficulty in establishing uniform criteria for evaluating a case. For example, the age of onset and from it the duration of squint are considered to be of prime importance as to the prognosis for a functional result. Those of us who see a large number of strabismus cases realize how difficult it is to determine accurately the age of onset. Parents frequently state the eyes have been crossed since early infancy but on examination one finds little evidence of sensorial adaptations, suggesting a much later onset. Conversely, parents will swear that the eyes were straight until a few days ago but examination will show marked sensorial adaptations, suggesting a much earlier age of onset. Was the first case an example of pseudostrabismus due to epicanthus or a low wide bridge of the nose that recently developed a real strabismus? Was the second case an instance of a small angle esotropia held straight by peripheral fusion until the recent onset? These are but two of the many difficulties that beset the analysis of the results of treating strabismus. Only when we have obtained ways of eliminating and standardizing these variables will we be able to compare results and arrive at an unanimous choice of the correct surgical procedure and the most propitious age for operating on a case of strabismus.

PHILIP KNAPP

THE EFFECT OF EARLY SURGERY FOR STRABISMUS ON THE PSYCHOLOGY OF THE CHILD

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The problems of the relation between strabismus and the psychic condition of the strabismus patient are very interesting but very slightly investigated up to the present. They may be considered under two aspects: (1) the psychic

troubles as etiologic factor of strabismus; (2) the strabismus as generator of psychic troubles.

In order better to understand the troubles connected with muscular equilibrium (that is to say strabismus) which occur as a consequence of functional changes of the cerebral cortex, the anatomo-physiologic basis of binocular vision should be considered. Since it is the cerebral cortex which actually controls the parallelism of the two visual axes in most cases, it is logical to consider the part played by psychopathy in the development of strabismus. The authors cite examples from the literature as well as their own observations to support this approach to the problem, stating that psychic disturbances can sometimes be the cause of squint.

On the other hand, strabismus usually causes functional neurologic disturbances and can seriously upset the psychic balance of such patients. This neuropathy is characterized by abnormal irritability combined with excessive exhaustion of the central nervous system. The majority of those disturbances are modified after the strabismus is corrected: this is the incontestable proof of their origin. As a rule, this modification is a positive one; gradually the children achieve a normal or almost normal psychic equilibrium in the postoperative period.

The correction of strabismus achieves a cure of its neuropathic sequelae as a rule. On occasion, however, it aggravates them. For this reason, the most logical approach concerning the psychic troubles caused by strabismus is prophylaxis. That is to say that strabismus should be corrected before it can produce the psychic upsets characteristic for it, before family and school surroundings arouse in the patient the consciousness of his infirmity. This can easily be achieved if on the one hand the family of the patient is educated and made to cooperate, and on the other hand if early surgery or orthoptic treatment are carried out in the pre-school period.

The majority of modern ophthalmologists does not consider age limits for the surgery of strabismus, and maintains that the age of 5 years or even earlier is desirable. The authors report on a series of 17 children operated before the age of 4, with excellent results in all cases.

Comment: There can be no doubt that psychic trauma may precipitate a case of strabismus. However, there is little evidence that psychic trauma is the actual cause rather than the precipitating factor. Also there can be no doubt that strabismus has a definite effect on the personality and behavior of the affected individual. The authors correctly emphasize the importance of preventing the psychologic consequences of strabismus by the early correction of the strabismus. This is certainly in agreement with our feeling that every child should have cosmetically straight eyes before beginning school.

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POST-OPERATIVE IRIS PROLAPSE, ITS CAUSE AND MANAGEMENT

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The authors state that prolapse of the iris may be considered an exaggerated form of the condition of flat chamber, caused by turgescence of the vitreous and delayed emptying of the chamber. They found it a rather common complication, most particularly after cataract extraction even when corneo-scleral stitches were applied. It was their experience in the 2 to 4 per cent of their cases that had prolapse of the iris that cutting and putting the pillars back into position did not yield very satisfactory visual results, and sometimes resulted in a complete basal iridectomy. Because cataract extraction is a socio-economic problem, every attempt is made to give the patient a normal 6/6 vision. Therefore, treatment by means of repositioning of the prolapsed iris, stitching of the wound, and antibiotic therapy was begun.

One hundred cases of iris prolapse, seen 2 or 3 days after cataract extraction, served as subjects for the study. Of these cases, 50 served as controls and received the usual treatment: cutting of the prolapse and repositioning of the pillars, the wound being closed with two stiches. The other 50 cases were treated by the following method:

The wound was opened and the prolapsed iris was put back into position. In these cases, the vitreous was always found either in the anterior chamber or in the wound. It was allowed to prolapse, and the chamber was irrigated with normal saline solution. The wound was then closed with three corneo-scleral stitches, and air was injected into the anterior chamber; 100,000 units of crystalline penicillin were injected subconjunctivally. Then 1 per cent atropine ointment was applied, and the wound covered with a pad and bandage. The patient was placed on a regimen of 1 per cent atropine-1 per cent erythromycin eye ointment twice a day until the condition was cured. If iritis developed, it was treated with 1 per cent atropine twice daily, hydrocortisone eye ointment every 4 hours, and intramuscular injections of butazolidine-amidoprine with 200 mg. of vitamin C on alternate days for a total of 4 to 6 injections. All cases received oral sulphonamide and intramuscular penicillin in adequate doses.

A general survey by the authors of their cases at S.N. Hospital, Agra, revealed that prolapse of the iris occurred most frequently in cataract extraction without iridectomy with one stitch (12 per cent), and in cataract extraction with peripheral iridectomy without stitches (7 per cent). Prolapse of the iris occurred in 5 per cent of those cases of cataract extraction without peripheral iridectomy with one corneo-scleral stitch under "pre-post-operative" acetazoleamide (sic), 4 per cent of those with peripheral iridectomy with one central corneo-scleral stitch, and in 1 to 2 per cent of those with peripheral iridectomy with 3 corneo-

TABLE 1

Method	Visual Results (%)						
	<6/36	6/36	6/24	6/18	6/12	6/9	6/6
Cutting of prolapsed iris	8	12	24	12	20	20	4
Authors' method			4	8	24	44	20

scleral stitches. Under the method outlined by the authors, no further prolapse of the iris occurred. The visual results in those cases treated by the authors' method and in the controls are shown in Table 1.

Iritis developed in 44 per cent of those cases treated by excision of the prolapse, as compared with 18 per cent by the authors' method; hyphema was present in 20 per cent of the cases treated by excision, and in only 6 per cent of those treated by the authors' method. Infection was nil in both groups.

The authors reject the argument that repositioning of the prolapsed iris is fraught with danger of fulminating and uncontrollable infections which may lead to loss of vision or of the eye *in toto*. They state that antibiotics and chemotherapeutic agents serve well as a presurgical cover.

The authors state that repositioning of the iris is the superior method of treatment because of the lessened rate of complications and the better visual results obtained, especially with regard to the degree of astigmatism experienced, which is often high in those cases in which the tissue of the iris has been cut either before or after prolapse. They recommend the method of repositioning of the iris for universal application to cases of this type.

Comment: The authors present a series of 100 cases of prolapse iris in which one half were treated by excision and one half by replacement. Their series proves very definitely the advantage of two or more corneal scleral sutures combined with a peripheral iridectomy. The authors probably do more cataract extractions in 1 week than the busiest ophthalmologist in this country does in a year.

Prolapse of the iris is always an annoying complication, but the reviewer cannot agree that it is always associated with vitreous in the anterior chamber or in the wound. In a round pupil extraction, if the prolapse is noted within 24 to 48 hours after surgery, an attempt can be made to reduce it with a spatula combined with an additional one or two corneal sutures. However if it does not replace easily, it should be excised. Should a complete iridectomy have been performed at the time of the original surgery, excision of the prolapse is the treatment of choice. In reoperating on an eye within 24 to 48 hours after the primary surgery one cannot use a retrobulbar block—the globe is tender and the patient apprehensive. Also when vitreous prolapses it is often difficult to stop it and irrigation of the anterior chamber may increase the prolapse.

The best treatment would appear to be the use of 2 or more corneal sutures combined with an iridectomy. One must not forget, however, that our fine needles and sutures may be too expensive to use when one has several hundred cataract extractions to perform on an indigent population.

P. ROBB MCDONALD

OCULAR SURGERY IN THE AGED

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Old age presents special problems in major ocular surgery. In an attempt to establish some general principles as to the feasibility of surgery and the risks it entails in patients over 65 years of age, the 118 major eye operations performed on the residents of the Home for Aged and Infirm Hebrews of New York during the last 15 years have been reviewed. The points considered were the type of operation, the preoperative medical status of the patient, his age at operation, the results of the operation, and the complications encountered, both local and general. Most of the operations (85) were for restoration of vision which had been lost as a result of cataract formation. Surgery was also used in 18 cases of glaucoma in which medical measures had failed. Four operations were performed for retinal detachment, and a small number of different procedures accounted for the remainder.

The results of the cataract extractions were extremely encouraging. In 59 (87 per cent) of 68 intracapsular cataract extractions there was vision of 15/70 or better as a result of operation. Vision of 15/70 or better was also obtained in 12 (71 per cent) of 17 extracapsular extractions. When both types of procedures are considered together, a total of 71 eyes (84 per cent) showed vision of 15/70 or better. This is sufficient to enable the patient to take care of himself.

Detailed analysis of the cases in which postoperative vision was 15/200 or less revealed adequate reasons for the poor vision; each patient showed pathologic changes not attributable to the operation, except for one case of severe vitreous hemorrhage. It is important to note that in these cases, with the exception of those of optic neuritis and vitreous hemorrhage, all the patients had a return of useful peripheral vision after cataract extraction. The full value of the vision provided by the retina outside of the macular area should be appreciated. Even though the macula is destroyed, the vision remaining in the rest of the field is sufficient to enable the person to carry on a reasonably self-sufficient and meaningful existence without being a burden to others. Consequently, even though visual acuity may be reduced by reason of macular damage, cataract extraction in this older age group is still definitely indicated when cataracts are present together with macular degeneration.

Most (16) of the cases of glaucoma were controlled with or without medication after surgery, but two were uncontrolled even after operation and went on to total blindness.

Despite the fact that many of the patients had the usual diseases found in

this age group, the number of patients with postoperative general complications was gratifyingly small: only 10 out of the total group of 118. Two of the 10 patients died, one of congestive heart failure and the other of acute myocardial infarction, but since patients in this age group are continually suffering incidents of myocardial infarction, pulmonary infarctions, and other emergencies, the question arises whether these deaths were actually due to the operation or whether they might not have occurred anyway.

Analysis of the postoperative ocular complications, which occurred in only 12 cases, supports the view that fear of these complications should not act as a deterrent to the performance of necessary ocular surgery in the aged. These older persons stand to gain a great deal by the restoration of vision in their declining years, and since the risks of operation have often been overestimated, physicians in general should approach this problem from a fresh viewpoint.

Comment: This interesting presentation proves that the elderly patient withstands ocular surgery very well. Actually no patient is too old to operate on providing he is mentally competent and able to appreciate the hoped for improvement in vision. There may be some contraindication to general anesthesia but if local anesthesia can be used, the patient has more to gain than lose. Surgery should be considered after full discussion of the situation with the patient or his family.

One should be very careful of the preoperative sedation. A test dose should be tried before surgery. The elderly patient frequently reacts poorly to barbiturates. Only one eye should be bandaged. If the patient is monocular, only a plastic shield should be used. Finally, the patient should be ambulated and encouraged to move about as soon as his sedation has worn off.

P. Robb McDonald

SHOES AS A POTENTIAL HAZARD TO SURGICAL AND OBSTETRICAL PATIENTS

A. E. Casey, H. Ferguson, J. G. Casey, A. Hogg, F. M. Schabel, Jr., E. A. Dowling, E. Grooms and J. Simmons

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It was observed that bacterial counts in the air of operating rooms frequently rose when the surgeon walked into the operating room. Since shoes could be the source of the air contamination, they were made the subject of a bacteriologic study.

Fifteen pairs each of obstetricians' and surgeons' shoes were cultured. These shoes were used only in the respective air-conditioned suites. Cultures from every pair of shoes had multiple colonies. More than 70 different strains of organisms

were isolated, including some 23 strains of hemolytic staphylococci, 5 strains of Proteus, 1 strain of Neisseria, 50 β-hemolytic Gram-positive rods and numerous fungi. Among the 23 strains of hemolytic staphylococci 5 were penicillin-resistant.

Thus a fertile reservoir of pathogens were encountered on surgeons' shoes used only in the operating suite—80 per cent of the shoes had hemolytic staphylococci, Proteus or other pathogens. With the reduction in humidity from air-conditioning, colonies of bacteria on such shoes may be thrown into the air and circulated in the operating or delivery suites.

Measures to reduce the hazard of bacterial flora on surgeons' shoes might include: washable shoes which could be placed in a washing machine at the end of an operation, sterile cloth shoe covers tied about the instep, and ultraviolet sterilization.

Comment: Although the incidence of surgical infections in ophthalmology is extremely low, the ophthalmic surgeon is anxious to be alerted to any unsuspected source of infection so that he may maintain or perhaps improve the excellent record.

The surgeon changes into a clean surgical shirt and pair of trousers and covers his hair with a cap and his face with a mask. It seems reasonable to go one step further and protect the shoe area. The measures suggested by the authors to reduce the shoe hazard deserve consideration.

LEONARD APT

WOUND HEALING

EDITORIAL

M. J. Australia, 1959, *2:* 223–225

Wounds, whether inflicted accidentally or by the surgeon, heal so frequently that many who are responsible for their care are apt to take for granted the wonderful processes of wound healing. Ambroise Paré was sufficiently truthful and modest to admit that God healed the wound, the surgeon's duty being to dress it. During the past 30 years or so, many research workers primarily interested in clinical problems have been turning to the basic sciences for methods of study, and several studies on the biochemical and histologic aspects of wound healing have recently appeared in the medical press. A review of these at this stage should be of general interest.

The epidermis is capable of rapid and complete regeneration. The cells which accomplish this come from the edges of the wound and from the epidermal appendages such as hair follicles or sweat glands. W. S. Bullough and E. B. Laurence[1] believed that the enormous increase in mitotic figures seen within a millimeter or two of the edge of the wound represented an exaggeration of the normal mitotic activity and not a qualitative alteration of cellular metabolism.

This mitotic activity is apparently aerobic, for it can be inhibited by enzyme poisons which inhibit respiration (W. W. Washburn[2] and P. B. Medawar[3]). At about the same time as the mitotic activity increases, the cells at the edges of the wound begin to migrate across the new surface. L. Loeb[4] showed nearly 40 years ago that the rate of migration was roughly proportional to the number of mitoses found in the resting epidermis. T. Gillman and J. Penn[5] have suggested that the epidermal changes have a dominating influence on the changes in connective tissue beneath. As maturation of the two tissues continues during and after healing, epidermal penetration of the granulation tissues occurs, and a realignment of the epidermis occurs *pari passu* with new collagen formation. One of the mysteries of nature which is a long way from being solved is this influence of one cell on another. The way in which one cell or group of cells influences another cell or group of cells is presumably brought about by cellular hormones, possibly nucleoproteins, but their precise nature and how they work remain a mystery.

During the second day after the infliction of a wound, fibroblasts in the dermis begin to appear and rapidly proliferate. Not long after their appearance the earliest signs of collagen deposition occur. However, before collagenous fibers are visible histologically the amorphous ground substance adjacent to the wound has the staining properties of acid mucopolysaccharide (J. E. Dunphy and K. N. Udupa[6]). This toluidine blue metachromasia reaches its peak in 5 or 6 days, and then rapidly declines (M. L. Stearnes,[7] S. B. Wolbach,[8] E. Kodicek[9] and Kodicek and G. Loewi[10]). It has been suggested that the mucopolysaccharide in the ground substance is responsible for the precipitation of collagen rods which are secreted in a soluble form from the fibroblasts (Stearnes[6]). Rudolph Virchow[11] was the first to suggest that collagen was secreted as a soluble substance and took on the characteristic fibrillation appearance outside the cell. The mucopolysaccharide concentration decreases as collagen formation increases. Dunphy and Udupa[5] suggest two phases of wound healing: first, the acquisition of the building blocks (mucopolysaccharides), and second, the collagen phase, which continues until the healing and contracture are complete. Protein-starved animals are unable to accumulate mucopolysaccharides as rapidly as normal, but the delay may be partially reversed if these protein-depleted animals are fed methionine. J. F. Morgan and H. J. Morton[12] showed that the activity of fibroblasts was related to the sulphur-containing amino acids, such as methionine. They pointed out that the intact animal probably converted methionine to cystine and that this conversion was accompanied by fibroblastic growth. According to M. B. Williamson, T. A. McCarthy and H. J. Fromm,[13] there is a direct correlation between increasing tensile strength of a wound and the sulphur content of the granulation tissue.

B. L. Reynolds, J. B. Codington and R. W. Buxton[14] have investigated the effect of the addition of a co-enzyme, adenosine-5-monophosphate (A5MP), on the biochemical aspects of wound healing. They found that the delay in wound healing which usually follows protein starvation or steroid administration could be diminished by A5MP. In other words, the collagen production is as-

sisted by the A5MP, this effect probably being brought about by cellular energy reactions and synthesis. As a result of their work they postulate that adenosine-5-monophosphate may effectively reduce the lag period between the infliction of a wound and the commencement of healing. J. F. Prudden, G. Nishihara and L. Baker[15] have shown in experimental wounds in the rat that the tensile strength of the wound in the early stages of healing may be increased by 20 per cent if the wound is treated with powdered bovine cartilage. There appears to be some connexion between Prudden, Nishihara and Baker's work and the importance of the mucopolysaccharides cited above, because cartilage is a good source of these building blocks. The tensile strength of healing wounds is very largely dependent on the adequacy of the returning collagen. The studies cited indicate some of the mechanisms involved in collagen production. Irritation in the substance of a wound, especially if giant-cell reaction is produced, delays fibroplasia and collagen-fiber formation (J. A. Schilling, B. V. Favata and M. Radakovich,[16] and Hans Selye[17]). The effects of wound sepsis and retained foreign body on wound healing have been observed clinically for a long time. Catgut produces such a reaction, and it has been suggested that the ideal suture material would be nonabsorbable inert thread.

The healing of most wounds is accompanied by a greater or lesser degree of contracture. H. Grillo, G. Watts and J. Gross[18] have studied the biochemistry and anatomy of contracture in wounds. These investigators attempted to relate the collagen (hydroxyproline), glucoprotein, mucopolysaccharide, tyrosine (noncollagenous protein), water and total tissue weight to the contraction of healing wounds in guinea pigs. Although they showed a rapid increase in the total wound content in the first 5 to 8 days after wounding and an equally rapid fall after about the 10th day, the rate of contracture continued at an even pace throughout. Consequently, there did not seem to be any relationship between these substances in the wound and the occurrence of contracture. Contracture of the scab may well be due to dehydration, but the water content of the wound itself was found to be independent of the contracture. These workers found in their dissections that the advancing skin edge was always firmly attached to a rim of newly formed tissues; if the edge became detached, retraction occurred. This finding stimulated the same team, G. Watts, H. Grillo and J. Gross,[19] to investigate the growing edge. They postulated a "mass migration" of a highly cellular matrix containing many fibroblasts deep to the healing edge, which draws the two sides of the wound together. However, the contracture is not a simple process; after the epithelium has closed the gap, it continues by shrinkage of collagen.

The processes of wound healing may be upset by a variety of local and general influences, including tension, apposition, paraplegia, resuture and nutritional deficiency. It has long been taught that the healing processes are hampered if tissues are repaired under tension. S. Borgstrom and P. Sandblom[20] showed that skin wounds healing under tension were weaker at 5 days than in the control rabbits. On the other hand, in rats, a wound of the abdominal wall had greater tensile strength if the animals were exercised. M. L. Mason and H. S.

Allen,[21] investigating the healing of tendons, found that although neater healing occurred with full immobilization, the tensile strength of the united tendon was greater if motion was begun 21 days after suture. These authors believe that the tension increased the strength of the suture after the exudative phase of repair was completed. B. F. Lounsbury[22] found that the tensile strength of a healed tendon was less if the muscle attached to that tendon was denervated. The steady pull of the normal muscle on the tendon suture increases the tensile strength of the healed tendon. R. C. Buck[23] showed that the effect of the pull was to produce an orientation of the cells along the axis of the traction. S. Thorngate and D. J. Ferguson[24] investigated the effect of tension on the healing of aponeurotic lesions. If the wound healed under tension, then the tensile strength was greater than if no tension was applied. The effect of the tension began on the 7th day and reached a plateau by 3 weeks. If tension was applied 7 days after injury, then the effect was the same as if it had been applied from the beginning. The next factor is apposition. Needless to say, if tension is so great as to separate the wound edges, the tissues will take longer to heal. Highly specialized tissues are capable of regenerating if the component parts are very accurately apposed. D. S. Jones[25] has investigated the repair of skeletal muscle in the dog. The union is first accomplished by fibrous tissue; then, after about 3 months, muscle fiber regeneration virtually eliminates the scar. However, the accuracy of apposition required to produce this muscle regeneration is not often found clinically. The same meticulous apposition of divided nerves has been the main tenet of nerve suture for many years. On the question of paraplegia, S. A. Loculio, E. W. Lowman and J. Gibson[26] have found, contrary to expectations, that the paraplegic patient can heal a wound as well as a normal patient. The failure to heal of decubitus ulcers is due to repeated trauma to anesthetized skin, not to failure of healing powers. Lesions on the feet in long-standing diabetes with gross neuropathy have the same difficulty, with the added disturbed metabolism, although the latter may be much less important than we used to think. Investigating the effect of resuture, E. D. Savlov and J. E. Dunphy[27] and T. W. Botsford[28] have shown that the normal lag period which follows an injury before healing commences does not occur if a wound disrupts and has to be resutured. The last of these factors is nutritional deficiency. M. W. Kobak, E. P. Benditt, R. W. Wissler and C. H. Steffee[29] have demonstrated that protein deficiency interferes with wound healing, and, as we have seen, the sulphur-containing amino acids have a role in some stages of healing (S. A. Loculio, M. E. Morgan and J. W. Hinton[30]). R. Sisson, S. Lang, K. Serkes and M. D. Pareira[31] have tested the tensile strength of wounds in rats in various stages of acute and chronic malnutrition and found that the tensile strength decreased with the body weight. Resuture of deliberately disrupted wounds under protein deprivation shows that there is no lag period in healing at second suture.

The studies reported above show only a tiny fraction of the immensely complicated biochemical machinery which comes into action when a finger is pricked or a child scratches his knee. In the future such work may enable the surgeon to control the healing of a wound and the amount of scar tissue which results.

Further, if the way in which one collection of growing cells "talks" to its neighbors could be understood, then some of the crucial problems of neoplasia would be well on the way to solution. The neoplastic cell is deaf to the "talk" of his neighbors which should restrain unruly multiplication. L. C. Edwards and J. E. Dunphy[32, 33] recently published a review of the present knowledge available on wound healing. Their papers are well worth careful study to anyone interested in this problem, and will indicate something of the extent of a major field of surgical research. These are certainly exciting times for the surgeon. We in Australia should see to it that our young men with ideas are encouraged to study these fascinating problems.

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Comment: This is a clearly written, well thought out, critical evaluation of advances in our understanding of the fundamental processes involved in wound healing. The author's emphasis on the importance of cellular enzymes in the synthesis of connective tissue components focusses our attention on the basic aspects of wound healing in contrast to the more obvious and practical phases which have been dealt with so adequately in the past. The influence of physical factors, such as tension, apposition, as well as innervation are, however, of particular pertinence to the practicing surgeon. Unfortunately, this excellent discussion deals mainly with wound healing in nonophthalmic tissues. In recent years considerable advance has been made in our understanding of the fundamentals in wound healing of ocular tissues. It has been demonstrated that before the appearance of the first connective tissue fibers, a narrow zone bordering the incision is an area of great mucopolysaccharide synthesis. These components have been found to be necessary to the synthesis and orderly arrangement of the connective tissue framework. Investigations in corneal wound healing have contributed greatly to our understanding of complicated processes involved in this synthesis. It is evident that in this tissue, and by implication in others, an important synergistic relationship exists between the epithelium and stroma. The presence of the corneal epithelium has been shown to be necessary to the synthesis of the ground substance and to the formation of new fibers. The reaction of connective tissue cells in the cornea to the stimulus of an incision has been followed during the first few hours after injury in which a sequence of proteolytic enzymes has been shown to appear and to activate the process leading to the differentiation of active fibroblasts from invading blood cells and preexisting keratocytes. These few examples of advances in our knowledge of this important field may be cited together with this well-written resumé of our knowledge of healing.

GEORGE K. SMELSER

RETINAL CIRCULATION

HYPOTENSION OF OCULOCARDIAC REFLEX*

Clinical Anesthesia Conference, New York State Society of Anesthesiologists, New York, New York

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The oculocardiac reflex, commonly observed during anesthesia, is produced by pressure on or traction of the eyeball. The cardiac reaction may vary from a minimal bradycardia to cardiac arrest.

Case 1. A 14-year-old girl was operated upon for internal strabismus. Following premedication with meperidine 50 mg. and scopolamine 0.4 mg., thiopental 300 mg. and nitrous oxide and oxygen were given for anesthesia induction. Intubation was facilitated with succinylcholine and an intravenous drip of the same drug was continued. With traction on the recti muscles an abrupt bradycardia and hypotension were noted. Release of the traction restored vital signs. To facilitate the progress of the procedure atropine 0.2 mg. was given intravenously. Traction applied 5 minutes later produced no further effect.

Case 2. A 50-year-old woman undergoing hysterectomy received morphine 8 mg. and scopolamine 0.3 mg. as premedication. Anesthesia was induced with Evipal and maintained with cyclopropane-oxygen. When the peritoneum was opened, a reduction in pulse rate and blood pressure was noted. The operation was stopped momentarily and the retractors released, but no improvement resulted. It was then noted that the face mask was pressing on the eyeballs. The mask was replaced by a smaller one. There was an immediate restoration of vital signs with no further circulatory changes.

Comment. The anatomic pathways of this reflex are thought to involve the ophthalmic branch of the fifth cranial nerve on the sensory side and then the cardiac vagal nerves, with the relay in the central vagal medullary centers. While hypoxia and hypercarbia have been incriminated as etiologic factors, the reflex is still active in their absence. The use of atropine intravenously in adequate doses has proved to be an effective form of therapy.

A preoperative clinical test is recommended to determine if eyeball pressure for 10 seconds reduces the pulse rate 10 beats or more. If it does, larger premedicant doses of anticholinergic drugs are recommended, together with careful monitoring of heart rhythm during surgery.

Comment: Death in the operating room is all too frequently, and often unjustly, attributed to reflex phenomena, while subfatal reflex hypotension goes unrecognized, untreated, or incorrectly treated.

Hypotension as a result of Celiac Plexus Reflex, Carotid Sinus Reflex, Vagal Reflex and Oculocardiac Reflex has long been recognized. When the cause, usually pressure on or

* From Survey of Anesthesiology, 1959, *3:* 424–425, 426.

other stimulation of nerves or a plexus, cannot be removed because of surgical demands, local block of the nerve or plexus with procaine or lidocaine is usually efficacious. If local block is inadequate or technically impossible, the intravenous administration of a cholinotropic drug, such as atropine, is usually effective. Vasopressors and blood transfusions are not indicated and may prove dangerous.

WILLIAM O. MCQUISTON

THE DIAGNOSIS AND TREATMENT OF NON-TRAUMATIC CEREBROVASCULAR "ACCIDENTS"

WITH SPECIAL EMPHASIS ON INTRACRANIAL HEMORRHAGE AND THE "COMMON STROKE"

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Pennsylvania M. J., 1959, *61:* 1190–1197

A stroke is a symptom complex of varied etiology. The most frequent causes are cerebral hemorrhage, cerebral thrombosis, cerebral embolism and brain tumor. As treatment depends upon the differential diagnosis the following studies should be considered in these patients: careful history and physical examination; neurologic examination; examination of size and reaction of pupils; examination of the eyegrounds for arteriosclerosis or spasm of the arterioles, hemorrhage or exudates in the retina, choked disks; laboratory studies of spinal fluid; x-rays of skull for evidence of the shift of the pineal gland; and, if necessary and after careful deliberation, cerebral angiography. Electroencephalograms aid in evaluating convulsions and tumors but are of no help in differentiating between cerebral thrombosis, embolism and hemorrhage.

Spontaneous intracranial hemorrhages are of two types: subarachnoid and intracerebral.

Subarachnoid hemorrhage is usually due to a rupture of a congenital aneurysm of the circle of Willis at the base of the brain and usually occurs in patients under 50 years of age. An aneurysm, ptosis of the upper lid, dilation of the pupil and an external squint frequently develop on the side of the headaches. Diagnosis is confirmed by blood in the spinal fluid and therefore spinal puncture must not be delayed. Because death may occur during the first attack in one-third of these cases it is important to do angiography bilaterally within 24 hours to locate the aneurysm and decide whether surgical therapy is indicated. The ideal surgery for an aneurysm is its obliteration intracranially by clips if its location permits this with a chance of avoiding aphasia or paralysis. If the aneurysm is in the

dominant hemisphere, ligation of the common or internal carotid artery in the neck may be advisable. Since these patients often have increased intracranial pressure the fluid intake, by Levin tube or by vein, should approximate the fluid loss and usually not exceed 2000 to 2500 cc. in 24 hours. Headache is treated with ice compresses, aspirin or codeine. Narcotics should be avoided because they caused marked respiratory depression.

Intracerebral hemorrhage may occur suddenly if a large vessel ruptures and over days if a small vessel breaks. In the latter event the eyegrounds may show flame hemorrhages and signs of hypertension or choked disk. The spinal puncture shows a clear fluid under high pressure if the bleeding has not trickled into the subarachnoid, and pinkish or red if it has. X-ray of the skull may show a shift of the calcified pineal gland away from the side of bleeding. Medical treatment is similar to that for subarachnoid hemorrhage. Reserpine intramuscularly, mecamylamine, chlorpromazine or lowering the body by refrigeration to 96° or 94°F. may be used to reduce the hypertension. If the bleeding is petechial and does not increase, the patient will probably recover without surgery. Operation is contraindicated if there is serious irreversible renal, cardiac, or pulmonary involvement and is not advisable if the massive hemorrhage is on the side of the brain which controls speech because this will usually cause aphasia. The author performed craniotomy on 32 patients with a mortality rate of 35 per cent. Although most of the patients who had the hemorrhages in or about the internal capsule causing paralysis of the entire side, were left after operation with a permanent paralysis of the hand and some movement of the arm, there was much recovery in the leg and most could walk with either a cane or a foot brace.

In *cerebral thrombosis*, headache is infrequent, and hypertension is not as common as in cerebral hemorrhage. The eyegrounds may show arteriosclerotic changes but hemorrhages are absent. The spinal fluid does not show hemorrhage and the pressure is usually normal. X-rays of the skull reveal the calcified pineal gland in the midline, or displaced if there is massive edema of the brain. Anticoagulants should be used with caution as petechial hemorrhages frequently occur in the area of the brain softening in the field of a thrombosed artery. If gross hemorrhage has been ruled out the use of a vasodilator such as carbon dioxide is justified. Papaverine hydrochloride should be given intramuscularly in doses of 100 to 200 mg. every 6 hours for the first 48 hours. The efficacy of stellate block is questionable, but if it is used it should be done within 12 hours of the onset of the stroke and *by one skilled in the procedure.*

Cerebral symptoms simulating a stroke can also be produced by occlusion of the carotid artery. The picture may vary from that of a "little stroke" to blindness on the side of the thrombosed vessel and complete paralysis on the opposite side. Diagnosis is established by angiography, by measurement of the pressure in the central artery of the retina, by opththalmodynamometry, by absence of hemorrhages in the eyegrounds, normal position of the pineal gland and clear spinal fluid. The treatment is similar to that for cerebral thrombosis.

In *cerebral embolism* the stroke is usually associated with some cardiac con-

dition. The onset is sudden and the clinical picture and treatment similar to those of cerebral thrombosis.

A slowly progressing "stroke" may be the early symptom of a *brain tumor*. A parasagittal meningioma involving the foot center of the brain can produce a foot drop on the contralateral side. If a unilateral convulsion occurs the chances are that it is caused by a tumor rather than a cerebrovascular accident. Any individual having a slowly progressive weakness in one extremity should be given the diagnostic survey described at the beginning of this paper.

While a patient is recovering from a stroke the treatment should include bedside therapy of the paralyzed extremity, treatment of speech defects and management of the individual as a whole for ambulatory and livable life.

THE CLINICAL MEASUREMENT OF RETINAL ARTERIAL PRESSURE

Richard B. Perry and John C. Rose

Circulation, 1958, *18:* 864–870

Physicians have always considered the retinal blood vessels important in diagnosis, but only since Baillart in 1917 designed the ophthalmodynamometer has it been possible to measure retinal artery pressure. Originally used only by ophthalmologists, the method has recently been found useful in diagnosis of thrombosis of the internal carotid artery.

The present study was based on 31 healthy persons with normal systemic arterial pressure, 41 with varying degrees of systemic hypertension, and 37 with evidence of neurologic vascular disease. In the first two groups, systemic pressure was taken in one arm, the intraocular pressure was taken with the Schiøtz tonometer, the ophthalmodynamometry was performed, and the systemic pressure taken in the other arm. Pupils were dilated when necessary, and local anesthesia applied in all cases. Blood vessel changes were evaluated for hypertension and arteriosclerosis, and in four cases systemic pressure was monitored by recordings from needles in the femoral arteries. Retinal diastolic pressure was read in the same way in patients with neurologic disease. Thirteen who had differences in pressure in the two eyes of over 15 per cent or clinical signs of thrombosis of the internal carotid also had carotid arteriography. Retinal readings were made with the patient supine, the plate of the instrument applied to the lateral surface of the globe. When intraocular pressure attained the level of retinal artery pressure, retinal diastolic pressure was maximal, and indicated by pulsation of the artery. Systolic pressure is measured by pressing the eyeball until the pulsation stops. Since the latter procedure causes slight intraocular hypotension, it should not be repeated for a half hour. Several measurements of diastolic pressure can be taken in rapid succession. In the present study only

diastolic readings were taken since these are generally more reproducible and systolic pressure often exceeds the upper limits of measurement of the instrument.

Studies of 75 patients with normal intraocular pressure indicated no significant differences between uncorrected and corrected readings, therefore the uncorrected readings were used in the rest of the study. The ratio of retinal artery to brachial artery pressure was studied, with averaged pressures of right and left eyes. Retinal artery pressure averaged 78 per cent of brachial artery pressure for the entire 75 patients, but 73 per cent in normotensive and 81 per cent in hypertensive persons. Absolute differences averaged 20.4 mm. Hg for the entire group, 19.5 mm. Hg in normotensives, and 21 mm. Hg in hypertensives.

In 75 patients with average retinal arterial diastolic pressures within normal limits, differences between the right and left eye were between 0 and 14 per cent; the mean difference was 3 per cent. The use of the ophthalmodynamometer did not affect systemic blood pressure readings taken simultaneously.

Of 37 patients with neurologic disease, 25 had recent or old hemiparesis and 3 had recurrent syncope, blurred vision, or aphasia. Seven of these had differences between retinal artery pressure in the two eyes of more than 15 per cent, with a range of 17 to 30 per cent and an average of 25 per cent. Thirteen patients, including the seven with retinal artery pressure over 15 per cent, had arteriograms. Six who had normal arteriograms had arterial retinal pressure under 15 per cent. Five others showed marked narrowing of the interior carotid artery, and one was diagnosed as pulseless disease. The reason for the pressure in the seventh was not determined. Literature of interest to the study is reviewed.

Comment: This article is one of the definitive studies on ophthalmodynamometry in occlusive disease of the carotid artery; 31 normal and 44 hypertensive patients were examined. An additional 37 patients with varying central nervous system disease were measured. All measurements were made in the supine position and only the diastolic retinal artery pressure (RAP) was recorded.

Of real significance is the fact that of the 37 patients with central nervous system disease, 13 patients were chosen to have subsequent carotid arteriograms. Seven of these 13 patients had a 15 per cent or more difference in their diastolic RAP, whereas the other 6 patients had clinical states suggestive of occlusive carotid disease. The 6 patients with negative ophthalmodynamometry, (difference in RAP less than 15 per cent) had no occlusion of the carotid system. Of the 7 patients with positive ophthalmodynamometry (greater than 15 per cent difference in RAP) 6 patients had angiographic proof of occlusive disease of the carotid arterial system. The final seventh patient had a tumor in the region of the ipsilateral internal carotid artery. These figures speak for themselves and are in agreement with current figures throughout the country. They indicate the validity and clinical application of ophthalmodynamometry in occlusive disease of the carotid artery.

The authors show definitely that there is a linear relationship between the diastolic RAP and the diastolic brachial artery pressure in 75 patients. From this we can see that any measurement of the RAP which does not include consideration of the systemic blood pressure is valueless for an absolute comparative analysis.

It is also comforting to note the authors' agreement that it is not necessary to use the conversion tables of Bailliart and Magitot in converting grams of water to mm. Hg. Convergence factors are unnecessary in subjects with normal intraocular pressure, and there-

fore both systolic and diastolic RAP can be read directly from the Bailliart instrument, assuming mm. Hg to be about 5 mm. greater than the absolute reading.

The value of this article lies in the fact that after obtaining normal RAP measurements the authors were able to confirm the presence of occlusive disease of the carotid artery by corroborative carotid angiograms.

JOSEPH AMDUR

OBSERVATIONS ON OPHTHALMODYNAMOMETRY

J. LAWTON SMITH, IRVING H. ZIEPER AND DAVID G. COGAN

J.A.M.A., 1959, *170:* 1403–1407

The usefulness of ophthalmodynamometry in early diagnosis of internal carotid disease is indicated by the striking success of both medical and surgical treatment of the condition. Also Fisher's studies have revealed a high incidence of extracranial carotid artery pathology. Ophthalmodynamometry has been used as part of his studies of cerebrovascular disease, and has led to some useful observations which are reported in this paper.

Using full mydriasis and topical anesthesia, the observer watches for the appearance of retinal artery pulsation as an assistant exerts pressure against the eyeball with the Baillart ophthalmodynometer. Observations are checked three times. Reproducible differences in artery pressure between the two eyes of 10 units systolic or 6 units diastolic are significant when systemic pressures are within normal limits.

Since some patients with occlusive carotid artery disease may note amaurosis fugax or other ischemic changes related to posture changes, we investigated differences in retinal artery pressure in the supine and standing position, and found that study of the artery pressure in the two positions did disclose significant differences not necessarily discovered by examination in one position only. In two summarized cases, either slight differences in artery pressure in the two eyes, or no difference, was observed when the examination was made supine; but with the patient in erect position, decidedly significant differences were evident. In one instance the reverse proved true.

While diastolic values are those usually given and may be sufficient when differences between the readings in the two eyes are significant, the importance of also taking the systolic retinal artery pressure has recently been stressed. Though no damage has been reported to date, this measurement should be taken rapidly. Two cases are reviewed in which diastolic readings were nearly alike in the two eyes, but the systolic readings were clearly different. The reverse has not been noted.

Anticoagulant therapy has markedly improved some cases of internal carotid artery disease. Our experience in two cases suggests that the change may be

partly explained by restoration of arterial pressure. In one case systolic pressure on the obstructed side rose 15 mm. Hg, and in another case low pressure on both sides was raised with clear improvement in symptoms.

In six cases of auricular fibrillation, we have found wide and variable range in both diastolic and systolic readings by ophthalmodynamometer. Apparently this method means little in these cases.

Ophthalmodynamometric measurements may be extremely useful in evaluating the results of carotid artery ligation or endarterectomy. In one summarized case, restoration of pressure after operation correlated well with arteriographic studies, and in a second case with persistently low pressure despite operation, arteriography also corroborated the ophthalmodynamometric reading.

This method of study is indicated in cases with clinical evidence of cerebrovascular disease, in cases of amaurosis fugax, in evaluation of the results of carotid ligations and endarterectomies and of anticoagulant therapy, and as a routine procedure before arteriography. Difficulty in obtaining reproducible results suggests cardiac arrhythmia.

Comment: This article is a study of ophthalmodynamometry using 11 illustrative cases of occlusive disease of the carotid artery. In the past 5 years, many conclusive studies have demonstrated that in occlusion and insufficiency of the carotid artery, the ipsilateral systolic retinal artery pressure (RAP) will be diminished by 20 per cent or more, whereas the ipsilateral diastolic RAP will be 15 per cent or more less than the RAP on the normal side.

The present study emphasizes the effects of posture in uncovering differences in RAP. The authors come to no conclusion as to whether the test should be done in either the supine or the erect position, but emphasize that measurements should be taken in both positions. This has not been done in a large series of cases, but the fact that successful cases have been uncovered by other investigators in both the supine and the erect position, indicates that pathology can be demonstrated from either position. It is logical that the number of false negatives uncovered will be greater if the test were done in both positions. The authors' emphasis on determining the systolic RAP as well as the diastolic RAP is well taken. In borderline cases when the diastolic RAP alone does not demonstrate a greater than 15 per cent difference, if a systolic reading has been done which demonstrates a 20 per cent or more difference, more pathology will be uncovered.

The authors' method of measurement of the RAP with indirect ophthalmoscopy and 2 observers is interesting, although I wonder if it is not unduly cumbersome for the average observer. Most investigators feel that an accurate measurement can be made with the Bailliart ophthalmodynamometer placed against the unanesthetized or anesthetized conjunctiva, and the pulsations of the central retinal artery observed through an undilated pupil with direct ophthalmoscopy. However, in myopic patients, patients with movement of the globe, or with opacities of the media, indirect ophthalmoscopy will enhance measurement of the RAP.

It would be more impressive had the authors proved that carotid occlusive disease existed in each of their illustrative cases by corroborative angiograms. Without this proof some of the cases with borderline RAP are questionable.

Of interest is the report that no known injury to the globe occurred in over 100 patients in whom both systolic and diastolic RAP measurements were made. This is in agreement with current experience; however, transient episodes of amaurosis have been recorded following systolic RAP measurements, and I think caution should be observed in one-eyed

patients in the older age group in whom atheromatous plaques may be present in the ophthalmic artery.

JOSEPH AMDUR

OBSERVATIONS OF THE FUNDUS OCULI IN TRANSIENT MONOCULAR BLINDNESS

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Neurology, 1959, *9:* 333

In addition to their intrinsic interest ophthalmologically, observations of the retinal circulation during episodes of transient blindness could be of importance in interpreting cerebrovascular events—especially transient ischemic attacks of paralysis, numbness, blindness, dizziness—that have been variously attributed in the past to vasospasm, fluctuation in the systemic blood pressure, progressive thrombosis, multiple embolism, or diminution in the intracranial circulation related to the upright posture, all of which remain untested hypotheses.

The vascular events underlying episodes of transient monocular blindness in a hospitalized patient were witnessed, possibly in greater detail than heretofore reported in the literature. The patient, a 54-year-old pharmacist, had a history of recurrent headaches, with some hypertension, for 10 to 15 years preceding hospitalization; right hemiparesis for 2 years, and a total of approximately 700 brief attacks of partial or complete blindness in the left eye for 1½ years. These attacks lasted for ½ minute to 45 minutes, gradually increasing in duration and frequency. In a partial attack, usually only the lower half of the patient's vision clouded over; in a full attack the vision was completely blacked out. There was no associated dizziness or lightheadedness and no apparent relationship to his headaches. In the few weeks preceding admission he had had transient monocular diplopia three or four times, each episode lasting 1 to 3 minutes. Ten days before admission he had an attack of numbness on the right side of the face, accompanied by complete loss of speech. On admission his only complaint was mild impairment of articulation.

Examination revealed slight right facial weakness, a trace of dysarthria, and a definite, although mild, reduction of position sense in the fingers and toes on the right. Pulsation was clearly reduced in the left internal carotid artery in the neck, and a left carotid arteriogram showed marked narrowing of the lumen within the carotid sinus. Skull x-ray showed demineralization of the dorsum sellae, and an electroencephalogram showed a mild abnormality consisting of

slow waves in the temporal regions bilaterally. Partial occlusion of the left internal carotid artery, associated with transient retinal ischemia and an old cerebral infarction, was the diagnosis. After treatment with Tromexan and Dicumarol, begun 12 days after admission, no further transient attacks of blindness occurred.

During the first 10 days in the hospital the patient had five attacks of transient blindness in the left eye, lasting 20, 60, 1, 30, and 65 minutes, respectively. During two of these attacks the retinal vessels were examined ophthalmoscopically.

The impression gained immediately on observing the vascular events was that a white material, immiscible with blood, was being driven distally along the artery. Some of the more important features, summarized, were:

1. The boxcar pattern and slow forward movement of the venous column of blood indicated that local stasis had taken place.

2. The white segment of artery was strikingly white and glistening, obscuring the pink background of the retina and the shadow of the vein passing beneath; at times its lateral borders seemed to have a double contour.

3. As the white segment migrated distally it seemed to be temporarily halted at bifurcations.

4. At 35 minutes (in the 60-minute attack) a trickle of erythrocytes seemed to run intermittently along one side of the white segment.

5. The interface between the red and white segments was always rectangular or transverse and did not taper off; no mixing occurred.

6. The forward movement of the red column and the simultaneous *en bloc* advance of the white segment seemed to point clearly to intravascular material being displaced distally by the oncoming blood. The consistency of the white material seemed to be about the same as that of blood, and it did not distend the artery. A puzzling feature of the whiteness was its gradual reduction in amount as it moved distally.

7. The majority of the patient's attacks apparently unfolded in a characteristic way, the ischemia distal to the obstruction repeatedly taking the same pattern.

8. The visual defect persisted for a period of 35 minutes after the circulation was maintained, suggesting that full functional recovery of the ischemic retina required an additional length of time and thus accounting for the apparent delay in return of vision.

In attempting to explain these events, the literature to date (which included 33 descriptions of retinal circulation during episodes of transient monocular blindness) was reviewed. Descriptions were so variable as to be almost impossible to classify. The most common picture is one in which the arteries are attenuated, reduced to threads, collapsed, or in spasm, or in which they have actually disappeared from view. The mechanism most often invoked in accounting for the retinal ischemia was vasospasm, but usually no underlying pathophysiologic process to which the spasm might be attributed was evident.

In the present case it was assumed that partial occlusion of the left internal

carotid artery within the carotid sinus was basically responsible for the repeated attacks of transient retinal ischemia and the episodes of cerebral infarction.

No conclusive interpretation of the vascular phenomena witnessed was reached. Vasospasm or excessive vasoconstriction did not seem to be factors, nor did it seem likely that the white segments were simply stretches of collapsed artery. The events suggested that whitish material, a microembolus, lay within the retinal arterial system and intermittently migrated distally. Possibilities that it was of lipid composition, a platelet mass, sludged blood, a fibrin clot, or an unusually extensive fragmentation of the arterial blood column were not considered altogether satisfactory explanations.

It is suggested that further observations of this nature may help unravel the essential mechanism of the attacks and may lead to an explanation concerning similar processes in other parts of the body.

Comment: The painstaking account of the ophthalmoscopic findings during two attacks of temporary blindness in a patient with unilateral carotid insufficiency is particularly welcome at a time when the literature has some comprehensive reports of this condition (Hollenhorst, Wagener *et al.*).

The type of fundus lesion described in this publication so far defies interpretation. It is really a matter of interpreting an optical phenomenon. The picture is clearly different from that of a spastic contraction. Spasms, arising as reflex spasms from intimal irritation perhaps as far back as the ophthalmic artery, may account for the temporary thread-like arterioles during such attacks as described in the literature in one group of cases.

The author, speculating upon various possibilities to explain most or all phases of the minutely observed fundus lesions in his case, inclines toward microembolism. He agrees, however, that it would not be easy to conceive of 700 attacks of microembolism occurring in more or less the same manner. Furthermore, would so frequently repeated embolisms not damage the intimal endothelium and lead to visible permanent lesions of the vessel wall after more than a year?

Your commentator is inclined toward the possibility of an unusually extensive fragmentation of the arterial blood column, invited perhaps by the lack of collapsability of the walls of the central artery within the central connective tissue strand and the cribriform plate during the period of markedly lowered pressure. A certain cohesiveness of the cellular elements in the slowly moving blood column within the retinal arterioles proximal and distal to the white stretch might prevent its mixing with the separated plasma portion (which seems to have occurred eventually in the more peripheral portions of the arteriolar tree), and thus retain the straight transverse demarcation line between blood column and white segment.

The peculiar linear advance of a single line of erythrocytes along one side of the white segment could be explained by hemodynamic forces, which also physiologically lead to different speeds of varying portions of the blood column (the axis current moving faster than the marginal portions). There could be a reversal of the usual forces under pathologic conditions leading to a more rapid marginal movement.

BERTHA A. KLIEN

UVEITIS

SPONDYLARTHRITIS ANKYLOPOIETICA ASSOCIATED WITH IRITIS

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Ann. Int. Med. Fenniae, 1959, *48:* 87–201

Spondylarthritis ankylopoietica is a generalized disease of mesenchymal tissue, which affects chiefly the sacroiliac joints and the lower part of the spine but may also occur in the peripheral joints and the insertions of tendons and ligaments. Involvement of other mesenchymal tissues has also been demonstrated. Iritis is regularly mentioned as a complication; in particular, nongranulomatous iritis is considered to be often associated with spondylarthritis ankylopoietica. Published reports on the incidence of iritis as a complication of spondylarthritis ankylopoietica vary greatly, no doubt as a result of differences in the length of the follow-up period, since iritis may occur at any stage of the disease, which often lasts for decades.

At the medical out-patient clinic of the Kivelä Hospital, Helsinki, since 1953, routine roentgen examinations of the spine have been made in all patients with iritis referred for an internal examination from the ophthalmic department of the hospital. A diagnosis of spondylarthritis ankylopoietica, which had rarely been diagnosed earlier or which had caused no noteworthy subjective symptoms, was made with unexpected frequency in these patients. The authors therefore undertook to examine systematically all patients with iritis in this hospital for the purpose of detecting the possible coexistence of spondylarthritis ankylopoietica.

On the basis of careful clinical and roentgenographic examinations of 134 patients with iritis examined in 1957, spondylarthritis ankylopoietica was diagnosed in 31 (23 per cent) and was suspected in 14 (10 per cent). The incidence was higher in males (32 per cent) than in females (13 per cent); for the suspected cases, the corresponding figures were 13 per cent and 7 per cent. The incidence of spondylarthritis ankylopoietica also increased with advancing age and was as high as 73 per cent in men aged 60 to 69 years.

Spondylarthritis ankylopoietica found in association with iritis may be at any stage of activity from the incipient, subjectively asymptomatic condition to the final stage of complete ankylosis. Only 3 of the patients had a history containing information on the presence of diagnosed spondylarthritis ankylopoietica. Ten patients had been treated for other rheumatic diseases. Follow-up examination of 6 of these patients, who had previously received treatment for rheumatic fever, failed to reveal rheumatic heart changes. It is possible, therefore, that the febrile polyarthritis in these patients was an acute phase of spondylarthritis ankylopoietica with symptoms from the peripheral joints. Examina-

tion of 4 other patients, previously treated for rheumatoid arthritis, failed to show the peripheral joint changes typical of that disease. In these patients, too, the previous disease was evidently an acute phase of spondylarthritis ankylopoietica, during which peripheral joint symptoms often predominate. Back pain had previously been present in 17 patients; thus, nearly half of the patients had been asymptomatic in this respect. Pain or inflammation in the peripheral joints or tendons without a definite diagnosis had previously occurred in 15 patients. In a large proportion of cases (nearly one-half the patients in this series), spondylarthritis runs a fully asymptomatic course. The disease may capriciously become arrested at a very early stage, and when this occurs even a thorough clinical examination will demonstrate no symptoms. Consequently, the diagnosis must be chiefly based on the roentgen examination.

Iritis may occur at any stage of the disease. In the present series, however, it was present more often in the cases in which roentgenologically visible destructive bone changes were present in the region of the sacroiliac joints or in the thoracolumbar spine. Although the roentgenographic changes do not always permit conclusions concerning the activity of the disease, the findings in these patients indicate that iritis usually occurs when repair is not yet complete. However, there were also cases in which bony ankylosis in the sacroiliac joints and a bamboo spine had already developed. In these patients, the disease process in the spine is evidently "burned out." There has been considerable controversy in the the literature as to whether iritis is a complication of spondylarthritis ankylopoietica, or one of the symptoms of a general disease of mesenchymal tissue. The present findings show that iritis and spondyl-arthritis often coexist, but that iritis may also occur when the active process in the spine is burned out. Thus they suggest that spondylarthritis and iritis have a common etiology and that they should probably be regarded chiefly as coexisting or consecutive manifestations of the same mesenchymal tissue disease.

Comment: Laitinen *et al.* state that iritis and SPA may occur simultaneously in the same patient and conclude that their data suggest a common etiology. This reviewer has recalculated the data on confirmed diagnoses of SPA in Table I and finds that SPA occurs in 11 per cent of patients with iritis under the age of 60, and in 23 per cent of patients above this age. This disparity would be expected if the diseases in question were unrelated, since the incidence of SPA, as the authors indicate, increases with age and in this same Table I the incidence of iritis is more than twice as great in patients under age 60 (152 to 60). To put it another way one should logically expect that if they are etiologically related the percentage incidence of simultaneous iritis and SPA should be reasonably close at all ages. The reviewer recognizes that using a statistical argument to criticize a statistical conclusion is unsound. He merely wishes to call attention to the hazard involved in assuming an etiologic or pathogenetic relationship between iritis and SPA on purely statistical data.

The authors have presented an excellent review of the clinical and roentgenographic features of SPA. They have called attention to an interesting and perhaps significant association of two diseases involving similar mesenchymal tissues simultaneously. However, final proof of similarity in etiology or pathogenesis, rather than random association, is not inherent in their data.

ROBERT S. COLES

GLAUCOMA

ÜBER DAS MYOPISCHE GLAUKOM (ON MYOPIC GLAUCOMA)

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Ophthalmologica, 1959, *138:* 302–307

The early diagnosis of chronic myopic glaucoma is extremely difficult and for this reason is rarely made in the early stages. (1) The papilla in highly myopic eyes is similar to glaucomatous excavation; the excavation is difficult to diagnose until it reaches the periphery of the papilla and the typical vascular picture can be seen. (2) The thin and less rigid sclera of the myopic eye does not respond to the tonometer in the same way as the nonmyopic eye so that normal or subnormal tensions are recorded even though the internal tension is pathologically high. (3) Estimation of the visual field is made difficult by the conus myopicus and the extensive atrophy of the retina and choroid. (4) The diagnosis of glaucoma is not thought of in the presence of high-grade myopia.

A 50-year-old woman who complained of deterioration of vision during the past 4 months was first seen in 1951. Vision of the right eye, after correction with −10.5 diopters was 0.9. The refractive media were clear. The color and level of the papilla were normal. The vascular conus was displaced a little toward the nose. The conus and peripapillary atrophy were typical. The macula was mottled. The pressure in both eyes was 18 mm. Hg (Schiøtz). The only suspicious symptom was in the field of vision of the right eye, a small crescent-shaped scotoma beside the enlarged blind spot. The water and caffeine test gave no further clue: the tension in the right eye increased 3, and in the left eye 2 mm. Hg. The daily fluctuation never exceeded 2 to 3 mm. Hg. Pilocarpin drops, once daily, were prescribed. Her eyes were examined at 3-month intervals over a period of 3 years, with no noticeable change in vision or tension. The Bjerrum scotoma had become larger and a contraction of 20° had taken place in the upper nasal quadrant. In 1955 she was admitted again because within the last 6 months her vision had deteriorated to 0.4 in the right eye and to 0.6 in the left. Tension fluctuated between 18 and 24 mm. Hg. The water-caffeine test was also negative. The deficiency in the field of vision had increased to 30° in the upper nasal quadrant, and also increased in the lower nasal quadrant and adjoined the scotoma. The visual field of the left eye corresponded to that of the right 4 years earlier. The papillae had glaucomatous excavations with a difference of 3 diopters to the right and 1.5 diopters to the left. Kettesy's cyclanemization diathermy was performed. The tension in both eyes dropped to values around 16 mm. In the 3 years since then the vision has reached 0.4 in the right eye after correction with −13 diopters and 0.6 in the left after correction with −12 diopters, and no other change has been observed.

This case was described in detail because the tension never exceeded the physiologic maximum, although the daily average tension showed a tendency to increase in the course of the years.

Two other cases are mentioned briefly. In one, in the initial stage, the only symptom was a narrowing of the visual field from nasal to about 20°. In the other the tension increased to 35 mm. Hg in 6 months, but returned to normal after cyclanemization. The function of the eye has not deteriorated within the year since the operation.

The prognosis of myopic glaucoma is more favorable the earlier the condition is diagnosed and the operation performed. Operation should be considered when the visual faculty deteriorates and the visual field becomes narrower, since the low tension is misleading.

Comment: The subject of this paper lends emphasis to the importance of the work of Hans Goldmann (Glaucoma, Transactions 2nd Conference Josiah Macy Jr. Foundation, New York, 1956, p. 137) in which he points out that the anatomic basis of glaucomatous excavation is the disappearance of the nerve and supporting glial tissue of the lamina cribrosa. The lamina itself bulges outward only at a late stage. In highly myopic eyes there is a temporal conus and often a nasal supertraction. The nasal supertraction prevents the nasal displacement of the vessels and the slant of the temporal conus shows only a thin area of tissue over the lamina. Therefore atrophic changes in the glial tissue are minimal and excavation does not occur until very late. Thus the ophthalmoscopic diagnosis is usually missed.

Tonometrically, the low scleral rigidity in myopia pointed out by the author is one of the reasons why the Schiøtz tonometer may give misleading results in myopia with glaucoma. The only way to avoid this mistake is to use Goldmann's applanation tonometer to measure the tension since this tonometer is not influenced by the scleral rigidity.

SAUL SUGAR

NEURO-OPHTHALMOLOGY

TWO CASES OF OPHTHALMOPLEGIA DUE TO BERG ADDER BITE

JAMES MONTGOMERY

Centr. Afr. J. Med., 1959, *5:* 173

Two cases of berg adder bite are described in which ophthalmoplegia was the outstanding feature. The berg adder (*Bitis atropos*) is a small viper found in the mountainous regions of South Africa and Southern Rhodesia. It has usually been considered to be relatively less venomous than other species of the viper family, but authorities differ in their opinions. The syndrome as observed in the two cases described does not seem to have been reported previously in southern Africa.

Both patients (a 21-year-old woman and a 19-year-old man) were bitten on the hand, and in each case only one fang had penetrated deeply. They both received first aid within an hour after being bitten. Both, however, developed bilateral ptosis and pupillary paralysis. Both complained of numbness or stiffness around the mouth and difficulty in speech. Systemic disturbance was absent and the local reaction to the bite, apart from swelling, was minimal. The optic nerves escaped involvement in both cases, and treatment with antivenene resulted in complete recovery of normal vision.

The clinical picture as noted in the two cases was compared with those described in cases of poisoning from other species of vipers. Berg adder venom apparently contains a proteolysin which causes local swelling by dissolving the tissue proteins, and a neurocytolysin which acts on the central nervous system—particularly the oculomotor and pupillary mechanism. These results are different from the effects of puff-adder venom, which causes intense local reaction, discoloration, and subsequent neurosis plus systemic disturbance due to hemocoagulation. The eye signs caused by the South American rattler (also a viper) have been summarized in the literature as impairment of vision or complete blindness and paralysis of both eyelids and eyeballs.

The observations in these two cases led to the belief that berg adder venom can cause a specific syndrome in the central nervous system and that more serious effects might result with a full dose.

UVEA

ASSOCIATION BETWEEN COLOUR OF THE IRIS OF THE EYE AND REACTION TO DENTAL PAIN

PHILIP R. N. SUTTON

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Nature, 1959, *184:* 122

An association between eye color and the reaction to pain from dental cavity preparation has been found to exist in Australians of European stock. The results are based on the examination of 403 consecutive patients whose teeth were prepared for filling by the cutting of their cavities with the Borden high-speed air-rotor apparatus. The patients ranged in age from 3 years to more than 50 years.

Pain reactions were classified as belonging to one of four categories: (1) no pain reaction during preparation of the cavity, (2) slight reaction, (3) marked reaction, and (4) so great a reaction as to require the injection of a local analgesic. The pain reaction values were arbitrarily designated as 0–3, and iris colors, ranging from blue to dark brown, were given values of 1–9. The association between pain reaction and eye color is considered significant, but due to joint association with other factors. The accompanying graph is based on more than 40 observations for each point, with the exception of the last three, which are for 11, 23, and 28 subjects respectively.

Judgment of pain reaction was based on 12 months' use of the Borden apparatus and on 20 years of clinical experience. It is acknowledged that both types of observation are open to criticism because of their subjective nature, but a test for the reproducibility of results was satisfactory, reexaminations 1 to 4 weeks after the original examination showing that of 136 subjects reassessed, the same value for eye color was obtained in 115, and for pain reaction in 114.

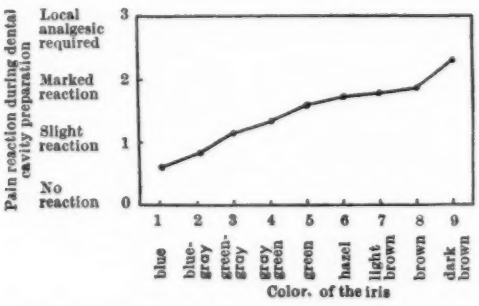

FIG. 1. Association between the color of the iris and the reaction to pain resulting from dental cavity preparation.

The mean of the discrepancy for pain reaction was 0.02, and for iris color 0.04.

Approximately 13 per cent of the total number of subjects required the injection of a local analgesic for cavity preparation. The percentage was the same for the pooled groups of those with grayish-green, green, or hazel eyes. None of the blue-eyed subjects required the analgesic, and only 2 per cent of those with grayish-blue or greenish-grey eyes required it. Thirty per cent of the subjects with light brown or brown eyes and more than 53 per cent of those with dark brown eyes required it.

Comment: One cannot help being intrigued by this alleged relationship between the color of an individual's iris and his or her reaction to painful stimuli. Perhaps this would also apply to ocular as well as dental pain and perhaps to other sensations besides pain.

IRVING H. LEOPOLD

MUSCLES

MACULAR DISEASE OF INVOLUTIONAL TYPE: CLASSIFICATION AND THERAPEUTIC APPROACHES

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Tr. Am. Ophth. Soc., 1958, *56:* 247–262

Involutional macular processes are generally a poorly defined group of central retinal manifestations with many overlapping morphologic descriptions complicated by a paucity of clinicopathologic materials and therapeutic specifics. All in all, they have been described as "one of the most annoying, depressing, and altogether discouraging conditions involving the sight" (Bedell, 1954).

This study deals with 164 patients with noncongenital impairments of macular function and appearance without acute exudative disturbances, trauma, cerebromacular involvement, tobacco-alcohol (vitamin-deficiency) amblyopia, disseminated retinal disease, central serous patterns or gross choroidal sclerosis. Only 10 of the patients were diabetics and in general they had mild cases with adequate control and little retinopathy elsewhere. Review of these 164 patients, including the manner of onset of their disease, the laboratory findings, and the clinical course, suggests that the classical or "primary" degeneration of the macula is by far the most common involutional process (75 per cent of cases) and that is is often associated with hypercholesterolemia. These cases seem to be rarely (4 per cent) complicated by macular hemorrhage in the nondiabetic

patient. Contrariwise, a hemorrhagic onset is fairly frequent (14 per cent) and often manifests a defect in the prothrombin mechanism. Consequently, patients in whom the onset is hemorrhagic should be classified separately and should receive more intensive hematologic study.

Other involutional lesions are classified morphologically according to their primary component. Cystic degeneration may occur entirely without hypercholesterolemia or associated sclerotic findings, proceed to hole formation, and show little tendency to overlap other involutional processes. Colloidal degeneration tends to be associated with increased blood cholesterol levels (as in primary senile degeneration), and to be more extensive in area and not associated with hole formation. Only one patient with a distinct, refractile pattern of crystalline involution was seen in this series. Two atypical, elevated, dark red "discoid" retinal lesions (not diskiform degeneration of Kuhnt-Junius) were seen in the right eyes of patients aged 35 and 54, with depression of vision to 20/30, improved to 20/20– in four months. A hereditary pattern has frequently been established for involutional disease in specific families, and the term heredodegeneration properly applied with adjectives indicating phenotype at a specific age, *e.g.*, juvenile, pre-senile, or senile. Genetic patterns, however, are generally beyond the scope of this study.

Treatment was approached on the basis of the classification described in the preceding paragraph. All patients were grouped on the basis of severity into mild (corrected vision 20/30 or better), moderate (corrected vision 20/40 through 20/80), or advanced (corrected vision 20/100 or worse). As controls, 26 untreated patients with 48 involved eyes were followed for from 2 to 5 years. Of these, 73 per cent had mild, 25 per cent moderate, and 2 per cent advanced involvement. Among the control cases observed for more than 2 years and the treatment cases followed for more than 1 year, 82 patients were seen for an average of nearly 3 years each. Within this observation, only 3 diabetic and 3 nondiabetic patients presented macular hemorrhages complicating previous involutional disease.

Prothrombin activity was found to be depressed to about half normal value in many of the patients in whom the onset was hemorrhagic. Vitamin K therapy was associated with improved prothrombin values in 6 of these patients, 2 of whom showed marked visual improvement; 3 other patients had similar and prompt visual improvement without demonstrable improvement in prothrombin activity. Lipotropic substances are apparently of value in about 12 per cent of patients with senile degeneration, and perhaps in a higher proportion of those presenting accelerated involutional changes within the period of a few months after cataract extraction. Intravenously administered heparin is also of occasional value in this connection, but it produced no change in 6 patients who had failed to respond to lipotropic substances.

Comment: One of the most interesting features of this study was the finding of a reduced prothrombin activity in some of the patients with hemorrhagic macular disease. Personally, I do not believe it possible that spontaneous hemorrhage exclusively in the macular

area without hemorrhagic tendencies elsewhere in the body could result from a depression of the prothrombin activity even to less than half of the normal value. Since the lesions were hemorrhagic, improvement of vision in some of these patients after treatment with Vitamin K, found by the authors, cannot be interpreted as a result of therapy.

Therapy to increase prothrombin activity in old people with a certain amount of arteriosclerotic disease could well precipitate occlusive vascular episodes, which would be particularly undesirable in the retinae of patients already afflicted with macular disease.

The role of Bruch's membrane in the pathogenesis of some of the deep hemorrhages was not mentioned. Breaks in this membrane which occur through as yet unknown alterations of the physical and chemical state of this structure, invite herniation and proliferation of choroidal capillaries through the breaks with irritation and injury to these vessels and subsequent transudative or hemorrhagic extravasations.

Even classification, let alone therapy, of these involutionary macular lesions is a most difficult task and awaits some results from the research laboratories which take a special interest in the region between the choriocapillaris and the percipient retinal elements.

BERTHA A. KLIEN

READING PROBLEMS

THE OFFICE MANAGEMENT OF PATIENTS WITH READING DIFFICULTIES

JOHN V. V. NICHOLS

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Canad. M.A.J., 1959, *81:* 356–359

There have always been children who were slow in learning to read, and the problem has probably been accentuated by teaching reading by the "flash" instead of the phonetic system. The sensory and perceptual processes involved in reading are complex, and consequently reading difficulty may stem from organic defects in vision or hearing or in the intellectual or perceptual levels related to vision or hearing, or from a nebulous region which integrates the hearing and seeing functions.

Many slow readers have superior intelligence, which is shown by exceptional facility in other subjects. Many are probably simply not ready to read at the age when they are sent to school, and the worry and pressure of parents accentuate reading difficulties in this group. In my series of 200 children, ten times as many boys as girls have reading problems, probably because boys mature intellectually more slowly than girls and are therefore more often unready to read at the age of 6. Probably boys have less retentive memories than girls, and possibly they need more to understand "how the thing works."

The latter characteristic may accentuate a boy's problems in reading if the phonetic method is not used. Also girls usually speak younger than boys and therefore have larger spoken vocabularies than boys of the same age, and vocabulary seems to be definitely correlated with facility in reading. Crossed dominance is not correlated to any notable degree with reading problems, but the poor sense of direction associated with crossed dominance may add to a reading difficulty.

Like Goldberg, the author finds a causal relationship between eye defects and reading difficulties is rare. The incidence of refractive errors or of extraocular disturbance is no greater in children with than without reading problems, but eye or visual defects may accentuate a reading problem.

The ophthalmologist, then, can contribute little directly by means of his professional skill, but he may be very helpful as an advisor and coordinator, if he is well informed on the needs of these children. Most of them respond to ordinary teaching, using a phonetic method, but the teaching must be done in an atmosphere of extreme patience and affection since these particular children seem very sensitive and in special need of affection. They require individual attention. It is very important that these problems be found and treated early before secondary emotional problems appear. About 2 per cent, however, have more severe problems which should probably be classed with aphasia.

The diagnosis of all but the simplest cases involves teamwork of several specialists, which can be co-ordinated by the ophthalmologist. The intelligence of the child should be assessed, realizing the limitations of the usual tests; positive results give useful information but negative results can be misleading. Psychiatric examination is useful in early, and probably essential in later cases, and psychiatric advice to the parents may be desirable in order tc prevent undue stresses. A thorough eye examination is regularly carried out, followed by glasses or any other indicated treatment if necessary. In instances of crossed dominance, drawing and hand-training exercises and permission to point at a line during reading, using the index finger, may be helpful. A complete survey of the child's hearing and auditory apparatus is also carried out, and hearing aids or special training by specialists are used when desirable. Usually these examinations show that the child is well within normal limits.

School training can often be supplemented by the parents. A number of useful books are available, and also various devices and word games. If the parents are either intellectually or emotionally unsuitable for helping the child at home, remedial reading classes should be available.

Comment: Children with reading difficulties are apt to be brought first to the ophthalmologist. It is more acceptable to the parents to think of a reading difficulty in terms of defective vision than in terms of, say, strephosymbolia. This word, with its connotation of disordered cerebral function, smacks of an intellectual defect (which it is not).

Nicholl's paper points up our obligation to our child patients with reading difficulties. This obligation does not end when visual defects have been ruled out. It is our duty to see to it that all factors are considered. These include defects in hearing, general intellectual defects, emotional disturbances and strephosymbolia.

Every specialist worth his salt must wage a constant inner battle against narrowness of outlook. Patients today are often coming to us self-referred. We should therefore see to it that they are directed to the proper person when the problem lies outside our own domain. Much of the present disenchantment of the public with physicians stems from the tendency of specialists to dismiss casually any problem which proves to lie outside their own limited field.

I would urge every ophthalmologist to read Orton's book.[1] It has intrinsic interest and is most helpful in understanding children with reading and speech problems.

REFERENCE

1. Orton, Samuel Torrey: *Reading, Writing and Speech Problems in Children*. W. W. Norton and Co., Inc., New York, 1937.

Owen Belmont

Pediatric Ophthalmology

ACUTE NEONATAL MAXILLITIS

B. Norgaard and J. J. Pindborg

Acta Ophthalmologica, 1959, *37:* 52–58

A 13-day-old girl was referred to the University Eye Clinic because of rapidly progressive proptosis and redness about the right eye of 4 days duration. When the globe was pressed a copious amount of pus exuded from the right nostril. Intraorally there was a swelling of the right alveolar process and sulcus with fistulae formation. A radiolucent area below the right orbit was seen in the radiograph of the maxilla.

The infant was given 50,000 units of penicillin intramuscularly for 28 days. When the *Staphylococcus aureus* and hemolytic Streptococcus organisms cultured from the pus were found sensitive to Aureomycin and Terramycin, oral Aureomycin, later parenteral Terramycin (because of bowel disturbance) was added to the therapy.

Initially the swelling in the oral cavity was incised. The following day the pus-filled cavity was curetted, and granulation tissue and two tooth germs were removed. An incision of the abscess of the lower eyelid was performed in the same day.

The origin of the infection was not established.

Proptosis and the swelling in the oral cavity subsided in 6 days but pus emitted from the oral cavity for 25 days.

Histologic examination of the two tooth germs revealed necrosis of the matrix and enamel, and an acute inflammatory reaction in the pulp with disorganization of the odontoblasts.

Examination of the infant 25 months later revealed a normal right eye, slightly retarded dentition, and a defect in the crown of an unerupted deciduous canine in the right maxilla.

Comment: This report describes a typical case of maxillary osteomyelitis with infection of the tooth-buds in a newborn infant. Proptosis is the outstanding presenting sign.

Since there is a distinct tendency for a localized infection to become generalized in the newborn infant, it is imperative that the proper antibiotic be given early, preferably by the parenteral route. Antibiotics taken orally are sometimes poorly tolerated by the gastrointestinal tract as was the case in the above report. Nausea, vomiting, or diarrhea further complicate an illness. In addition, there may be some difficulty in getting the infant to take the oral preparation (struggling, spitting, etc.), so that the exact dose of the anti-

biotic ingested is not known. This uncertainty and the possible gastrointestinal side-effects are best avoided when dealing with a serious or potentially serious infection in an infant.

Penicillin used alone at the start of therapy for neonatal infections would not be my drug of choice. Although the Staphylococcus is the frequent etiologic microorganism, the high incidence of resistant strains to this drug at present makes it much less useful. Furthermore, Gram-negative bacteria, also frequent causative bacteria in neonatal infections, are not eradicated by penicillin. Chloramphenicol is an excellent drug to use as the initial therapy in infections of the newborn infant until the results of cultures and sensitivity tests are known because it does not have these shortcomings.

(See "Chloramphenicol Dosage in the Newborn Infant. The 'Gray Syndrome' ", Surv. Ophth., *4:* 212, 1960.

LEONARD APT

Basic Sciences

MICROBIOLOGY

ISOLATION OF MEASLES VIRUS AT AUTOPSY IN CASES OF GIANT-CELL PNEUMONIA AND RASH

JOHN F. ENDERS, KEVIN MCCARTHY, ANNA MITUS AND WILLIAM J. CHEATHAM

New England J. Med., 1959, *261:* 875–881

Giant-cell pneumonia (Hecht's giant-cell pneumonia) is an interstitial pneumonitis characterized by the presence of multinuclear giant cells with ultranuclear and ultracytoplasmic inclusion bodies. Additional features include mononuclear cell infiltrate, proliferation of local cellular elements and occasional giant cells in other organs. The diagnosis has been dependent on histologic examination since 1910. Clinically the disease is a nonspecific pneumonia.

The etiology has been unknown although canine distemper virus and measles virus have been suggested because of their similar giant-cell formations, and vitamin A deficit because of similar epithelial changes.

Agents identified as measles virus were isolated from materials taken at autopsy from three patients with giant-cell pneumonia. None had signs or symptoms of typical measles during his illness. Identification was based on the similarity of cytopathogenic properties, growth patterns, infectivity for Macaca monkeys, characteristic lack of pathogenicity for suckling mice and chick embryos and antigenic composition.

These findings seem sufficient to indicate measles virus as the etiologic agent in at least a proportion of cases of giant-cell pneumonia.

Comment: The authors have shown that the measles virus may appear in yet another portion of the disease spectrum, by giant-cell formation in lung and other organs.

This organism is ubiquitous in distribution, highly infective but variable in degree of clinical manifestation, usually highly antigenic, and now has been shown to have a granulomatous potential. We are already aware of its ectodermal pathogenicity with skin, superficial ocular and central nervous lesions.

If one were to postulate a pathogen (an agent) which could satisfy most of the criteria as a cause of granulomatous (or a nongranulomatous) uveitis, a more suitable hypothetical organism could hardly be found.

MARTIN LUBOW

PATHOLOGY

EXAMINATION OF A SARCOMA OF THE UVEA BY ELECTRONIC MICROSCOPE

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Ophthalmologica, 1959, *137:* 65–73

The study of the ultrastructure of cells and tissues has become increasingly widespread in recent years; tumors, however, have but rarely been examined by electronic microscope. The malignant melanoma of the uvea appears especially suitable for this purpose, since the necessary material is easily available and the fragments can undergo fixation immediately after enucleation, an essential point for the study of cellular ultrastructure. It has been attempted to establish a relation between the degree of malignity and the histologic structure, considering the morphologic aspect of the cells, the quantity of reticulin present, and the degree of pigmentation of the tumor.

The authors intend to undertake comparative studies of the ultrastructure of malignant melanomas of the uvea with histological and clinical data. In this preliminary paper they describe the ultrastructure of a malignant melanoma of the choroid.

The cells show normal components in the electronic microscope, such as mitochondria, the granules of ribonucleoproteins, the vesicles of the cytoplasm, Golgi systems and the membranes of the ergastoplasm. On the other hand, they show some characteristic features, such as the compact granular structure of the nucleus, the spongy aspect of the nucleolus with its regular granular structure, and the numerous Pallade granules of the cytoplasm. The absence of virus-like formations should be noted. Such virus-like particles are found in the cells of a great many transmissible tumors. On more than 100 photos of the malignant melanoma which the authors examined, none of those particles were found. This will not, however, adequately support the conclusion that these formations are always absent in malignant melanomas and that viral etiology may be excluded. Other investigators have found them in one out of three cases only, and some in 60 to 80 per cent of the cases examined.

It is obviously impossible to arrive at conclusions on the strength of the study of one case or to express an opinion on the relation between the ultrastructure of the cells and histologic particulars on the one hand, and on ultrastructure and more or less pronounced malignity of the tumoral tissue on the other hand.

While the various structural elements found in the tumor cell are not essentially

different from normal cellular constituents, some of the particulars which were found are striking, since at least part of them are also found in other tumors.

It should also be taken into consideration that certain tumors can stay clinically benign for a number of years, up to 20 years and more, before they begin to proliferate. Other tumors develop intermittently. Reese (Tumors of the Eye, Hoeber, 1951, p. 219) offers two histologic arguments in favor of this opinion: (1) in many cases the malignant tumor is surrounded by a histologically benign zone; (2) the basis of the malignant melanoma is always found in the outward layers of the choroid, where the benignant melanomas are usually located.

Comment: Although only a preliminary report, this study is a forerunner describing a technique that will probably prove most fruitful. Ultramicroscopic studies of the various tissues of the normal eye has in only a short time, yielded most valuable fundamental information. Study of the ultra structure of the neoplastic cell, not only in ocular tumors, but in the whole gamut of new growths will surely add much to our knowledge of the nature of the intracellular characteristics of the cancer cell, with some possible explanation of its peculiar behavior.

T. S. SANDERS

PHARMACOLOGY

ATROPINE IN MONGOLISM

J. M. Berg, M. W. Gillian Brandon and Brian H. Kirman

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Lancet, 1959, *2:* 441–442

Sensitivity of mongol children to atropine has been observed at the Johns Hopkins Hospital, but no published reference to this observation has been found. The authors have from time to time used atropine as preoperative medication in mongolism, with no ill effects. But in view of its potential importance, the reaction of mongol children to atropine was investigated.

Two trials were made; in each there was a group of 10 mongols and of 10 mentally defective controls, matched for age, mental level, mobility, and general condition. Cripples and children with obvious motor lesions were excluded. In the two trials different patients were used.

One drop of atropine 1 per cent was instilled into the right eye of each child. The effect of the atropine drops was assessed in two respects: speed of dilatation at the end of a 15-minute interval, and duration of dilatation as noted during daily observations. As to the relative speed of dilatation, the mongols appeared to respond more rapidly to atropine than the controls ($\chi^2 = 5.597$, $p < 0.02$).

There appears to be a slight, though not statistically significant, relation between age and speed of reaction for the whole group. If the 11 patients under 7 years are excluded, then the significance of the difference between the groups rises ($\chi^2 = 7.146$, $p < 0.01$).

Table 1

Scores for Duration of Dilatation of Pupil

Trial 1		Trial 2	
Mongols	Controls	Mongols	Controls
39	15	24	13
24	6	25	30
44	17	38	20
27	12	25	36
37	16	31	38
31	14	49	22
23	24	37	33
21	24	40	17
26	29	35	29
	26	30	44
Total.....272	183	334	282
Mean.....30.2	18.3	33.4	28.2

TABLE 2
Analysis of Scores for Duration of Dilatation

Score	25 or More	24 or Less	Total
Mongols	15	4	19
Controls	8	12	20
Total	23	16	39

The possible relation between the low muscle tone, which is a constant feature of mongolism, and atropine sensitivity raises interesting speculation. Since atropine inhibits acetylcholine, which is concerned with normal stimulation of skeletal muscle, the two phenomena may be related to the same basic metabolic defect in mongolism. If atropine sensitivity can be confirmed by other workers, it may guide the development of rational therapy.

Further investigation of the statistically significant difference observed may throw light on the nature of the defect in mongolism.

The atropinized eye remained dilated for periods varying from 8 to 24 days. If the results of both trials are added, they are significant at the 1/20 level, though the second trial is not in itself significant. The speed of pupillary dilatation shows a difference significant at the 1/50 or 1/100 level, whilst the duration of dilatation gives a difference, the chance probability of which is 1/20. The results of these trials do not show a clear differentiation between the mongol and control groups. There is considerable overlap between the two groups, so that differences tend to be quantitative rather than qualitative.

Comment: This observation by the South African investigators that mongoloids show heightened reaction to atropine confirms an earlier observation of McKusick (1957) and suggests a clue to the defect of mongolism. The observation requires further confirmation and it is an important enough finding to warrant further investigation by ophthalmologists.

IRVING H. LEOPOLD

ACCIDENTAL ATROPINE POISONING

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Pennsylvania M. J., 1959, *62:* 1340–1341

A recent experience with atropine poisoning in a 40-year-old male patient was encountered after the patient frequently flushed his nasal passages with an atropine sulfate solution which had been prescribed for his dog. His symptoms

were characteristic of the condition, but the manner in which it was incurred was revealed only several hours after his acute problem required treatment.

The immediate therapeutic problem was to control extreme agitation: restraints had been required during transportation to St. Luke's Hospital. Sodium Amytal solution was administered by intravenous infusion and oxygen therapy commenced. Routine blood and urine studies were normal except for a mild leukocytosis (15,000 white blood cells per cc.). Fasting blood sugar and blood urea nitrogen tests were normal. The cerebrospinal fluid was slightly bloody, but the pressure was normal. This clinical pattern resembled a diffuse toxic encephalopathy.

It was estimated that the patient had used more than 50 mg. of atropine sulfate daily for several days, thus exceeding the average toxic dose. He may have come close to the average fatal dose of 100 mg. during the night before his acute illness.

The patient responded to sedation, oxygen therapy, and general supportive therapy. Within 12 hours his pupils reacted to light and he became responsive to conversation and his environment. After 6 days of hospitalization he was discharged in good health.

Comment: The symptoms of atropine poisoning rarely have to be pointed out to the ophthalmologist. "Hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hen" has been used by Kelsey as a description of this syndrome. The important thing is to be aware of what to do when such a complication is encountered.

IRVING H. LEOPOLD

ATROPINE POISONING FROM CONTAMINATED COCOA INGESTION

REPORT OF THREE CASES

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Pennsylvania M. J., 1959, *62:* 1324–1325

The most common cause of atropine sulfate poisoning reported is therapeutic overdosage. Other less common causes have been the use of atropine in suicidal attempts, the use of ophthalmic solution of atropine as intranasal medication, plasters containing belladonna alkaloids, and the ingestion of wild berries of *Atropa belladonna.*

Three patients were recently observed with atropine poisoning as a result of the ingestion of cocoa prepared in a contaminated flask. The three patients had been employed by a pharmaceutical company; the contaminated flask was used

in the manufacture of a preparation containing 6.6 gm. of atropine sulfate which was dissolved in 1920 cc. of hot water. After the flask was emptied, it was inadvertently placed on a rack containing sterile flasks. One of the patients used the soiled flask to prepare approximately 960 cc. of cocoa. The amount of atropine sulfate in the total mixture was estimated to be 576 mg.; the amount ingested by each patient was not known. All presented the clinical signs consistent with the ingestion of 10 mg. or more.

In the treatment of these patients universal antidote (a mixture of charcoal, tannic acid, and acid magnesium oxide) was administered by mouth and resulted in the patient vomiting three times. Sodium luminal 120 mg. and promazine 25 mg. were given parenterally for maniac outbursts. Intravenous infusion of glucose in normal saline solution was administered. When the respirations became more rapid and shallow, nasal oxygen was started with marked improvement. Intravenous fluids and nasal oxygen were maintained throughout the night.

Pilocarpine was not used for treatment, for several reasons: Death as a result of atropine poisoning results from central nervous system collapse and not from its peripheral effect. It was assumed that since atropine acts on the effector cells and increases the threshold of the effector cells to acetyl choline, the administration of a drug with an acetyl choline-like action would not be effective at the level of the effector cells, in the presence of severe atropine toxicity, unless given in toxic doses.

Recovery was uneventful in all three patients.

Comment: Fatalities from atropine and scopolamine are rare, although they have been reported. Of all the potent alkaloids, atropine has the widest margin of safety and, according to Goodman and Gillman, scopolamine is usually stated to be more toxic than atropine.

The diagnosis is usually based on widespread paralysis of those structures innervated by postganglionic cholinergic nerves. Of particular importance are the dry mucous membranes, the widely dilated unresponsive pupils, the cutaneous flush and fever, and the rapid heart. Most ophthalmologists are familiar with these symptoms. Occasionally they have seen patients, particularly after scopolamine, who have shown acute onset of bizarre mental and neurologic symptoms.

As the authors of this article stress, pilocarpine or cholinergic drugs may be given at intervals to make the mouth feel moist and add to the patient's comfort. A miotic can be instilled to overcome the cycloplegia and mydriasis. However, the central effects of the poison are not influenced by cholinergic therapy, and the essential aspects of the poisoning are the serious ones. Sedation is usually recommended to control the marked excitement. This can be done with barbiturates, paraldehyde or chlorhydrate but one has to be careful in the dosage administered because, in the late stages of atropine poisoning, depression is also present which can be compounded by the use of these sedatives. If depression does occur, central stimulants have to be used. Artificial respiration with oxygen administration may be necessary if severe respiratory depression occurs. Fortunately this is a rare complication of locally instilled belladonna group of drugs but some of our greatest contributions have been in our proper handling of these exceptional emergencies.

IRVING H. LEOPOLD

Book Reviews

Physiology of the Eye, by FRANCIS HEED ADLER. Ed. 3. $16.00. C. V. Mosby Company, St. Louis.

Since his student days in ophthalmology this reviewer has always enjoyed reading Dr. Adler's Clinical Physiology of the Eye. As the size of each edition has increased and the information presented become more complicated, the author's clear engaging, and informative style has persisted. The great advances in knowledge of the increasing number of conflicts has not disturbed the even tenor of the presentation which has made past editions as well as this one so readily understood.

There have been definite changes in this edition. The chapter on Ocular Muscles has been entirely rewritten and now includes a section on Electromyography. The section on Binocular Vision has been enlarged and the chapters on Aqueous Humor and Intraocular Pressure revised. In earlier editions the Cogan-Kinsey theory of corneal detergescence suggested that the intact corneas maintain a state of relative detergescence by virtue of hypertonic solutions in contact with anterior and posterior surface of the cornea. This is no longer tenable, and the author has presented the various experimental data of Maurice, Langham, Harris, Smelser and others which now leads to the presently accepted theory replacing the Cogan-Kinsey osmotic pump with a metabolic one.

As in any text which is published, there is much information which others may think should be included and by virtue of space limitation sometimes has to be omitted. Some of the recent work of Weimar on corneal wound healing is not included nor are some of the recent papers on tear analysis by McEwen *et al.*, Erickson *et al.*, Cassetti and Schumacher, Breunish, Krause and others. Nor does the author consider in the discussion of the vitreous humor the metachromatic staining cells recently reinvestigated by Balazs as well as others.

Dr. Adler has spent a great deal of his time teaching, studying, and investigating the various aspects of ocular motility, and this excellent text once again reaches its greatest height in the section dealing with this subject.

As in previous editions there are sections dealing with aqueous humor, intraocular pressure, light, metabolism of the retina, photochemistry of vision, electrical phenomena of the eye, the optic nerve and visual pathways, adaptation, sensory response, visual acuity, color vision, entopic and allied phenomena, as well as binocular vision.

The author has dedicated his book to Merkel Jacobs who introduced him to general physiology, to Cuthbert Bazett who gave him the opportunity to work in his laboratory, and to Alfred Newton Richards who taught him to be critical of

his own work. We are all indebted to Dr. Adler whose texts in ocular physiology over the past 20 years not only provides us with stimulating interest in this subject but also a delightful and easy understanding. There is no doubt that this third edition will continue to be not only a prominent part but a worn and well-thumbed part of the library of all ophthalmologists who are never satisfied with their present sphere of knowledge and are constantly striving to stay up to date.

IRVING H. LEOPOLD

Hypertension: The First Hahnemann Symposium on Hypertensive Disease, edited by JOHN H. MOYER, M.D. 790 pp. with illus. $14.00. W. B. Saunders Company, Philadelphia.

In December 1958, Hahnemann Medical College held a symposium on Hypertension. Background information on hypertension was reviewed, and many new ideas were presented by the investigators and clinicians who met together for discussion of developments in this field. Participants in the symposium were selected for their activities in those areas in which great advances have been made, especially in the past 10 years. Therapy is emphasized in this text. The symposium was divided in five sections: the first deals with the pathology and clinical aspects of hypertension; the second with the basic concepts of the etiology of this disorder; the third the pharmacology of hypertension and the use of sympathetic blocking agents; the fourth with the proper usage of salts and diuretics and special problems in the management of patients; and the fifth part is devoted to a discussion of the surgical approach to the management of various types of hypertension. There is much in this book of value to the ophthalmologist who is constantly reviewing fundi in patients with a predisposition toward or showing existing hypertensive disease. There are two specific chapters dealing with the eye. These are retinal vascular changes in hypertension by Albert Brust and the effect of blood pressure reduction on vascular changes by Walter Kirkendahl and Mark Armstrong.

There is a very lucid discussion of the pharmacology of the rauwolfia compounds, veritran alkaloids and hydralazine, ganglionic and adrenergic blocking agents which also will be of considerable value to the pharmacologically-minded ophthalmologists. The diuretic section deals mostly with chlorothiazide and hydrochlorothiazide which have little effect on intraocular pressure, although they do have some carbonic anhydrase inhibitory activity.

The section on adrenalectomy covers many of the aspects of the hazards of this procedure which is of interest to the ophthalmologist not only because of the influence of this surgical intervention on hypertension but of its considered value in patients with diabetic retinopathy so that the response of individuals to the procedure and the discusson of this shows one the proper respect which one must possess for this procedure in considering its potential value for any patient.

IRVING H. LEOPOLD

Symposium on Current Virus Research, Brit. M. Bull., Vol. 13, No. 3, Sept. 1959, Scientific Editor, C. H. ANDREWES. $3.25. The Medical Department of the British Council, 65 Divies St., London W1, England.

The British Medical Bulletin, in 1953, published an issue devoted to "viruses in medicine." This reviewed the developments up to that time of the medical aspects of the subject which is now generally called virology. This specialty has been advancing so rapidly that the present issue was produced only 6 years later. Most of the viruses discussed in the 1953 Bulletin are omitted in the present issue which deals mostly with adenoviruses, measles, varicella and trachoma. Enders, Robbins and Weller reported in 1949 that poliovirus would grow in cultures of tissues other than those of the nervous system and produced destructive changes which could be seen with a low-powered microscope. This allowed many new facts to be established quickly and quantitative serologic work became relatively easy. There became available a ready source of poliovirus resultive in the formalized vaccine. Antibiotics were helpful in this in that they kept down bacterial contaminations in the cultures. Many viruses remained difficult to study since no convenient experimental animal was available. Some of the human viruses such as measles and varicella can now be grown in cultures of human tissues and fresh advances have thus become possible.

In addition, these new tissue culture techniques have allowed numerous new viruses to be discovered. These include the adenoviruses, enteroviruses and new respiratory viruses. More than 70 new viruses have been discovered in the last few years. Most of these are of little or no importance in human disease so far. Each group of the viruses contain ones of different antigenic types. The fact that there are so many new viruses means that we have to rapidly expand our existing facilities for comparing and identifying these new viruses.

Virus genetics has become a very important subject.

Immunologic studies of viruses have been abated by agar gel diffusion techniques and the use of fluorescent antibodies, as well as by biochemical methods.

The discovery that the naked ribonucleic acid of some viruses can start infections is a recognized discovery of major biological significance. A most exciting new development of virology is the observation that one virus has the power to interfere with the development of another through the mediation of a substance, probably a protein, called interferon. It seems possible that the formation of this substance may be concerned in bringing virus infections to a halt in the absence of the normal immunologic mechanisms and, as pointed out by C. H. Andrewes, it is possible that further knowledge about interferon may lead to the discovery of what is so badly needed—a logically based chemotherapeutic agent active against virus infections.

Eighteen British specialists, all leaders in their fields, have contributed 15 well documented papers on new techniques and methods in virus research, discoveries of new viruses, and on genetic, biochemical, epidemiologic and epizoologic aspects of the subject. Eight full-page plates illustrate some of the techniques of the preparations described. There are very interesting notes on the contributors, their backgrounds, present positions and past contributions.

Although the ophthalmologist might be disappointed in not finding information on herpes simplex virus, he will be fascinated by many of the viruses touched on here—particularly the discussion of the relationship between chickenpox virus and that producing herpes zoster infections. The localized nature of zoster infections, the age group distribution and past history of chickenpox infection in many cases of zoster indicates that zoster is an infection with varicella virus in partially immune individuals. The demonstration by Weller and his colleagues that the varicella zoster virus can be readily cultivated *in vitro* may provide valuable techniques in the investigations of many unsolved problems relating to the pathogenesis of zoster.

The chapter dealing with interferon is a most interesting and stimulating one. The chapter on adenoviruses, which so frequently involve the ocular tissues summarized much of the information which is known about this group that was first described independently by a number of investigators in 1953 and 1954 in association with acute respiratory illnesses in military populations and in tissue cultures of human adenoids undergoing spontaneous degeneration.

The new serologic techniques in the field of virus research described by Belvabin considers the direct flocculation of viruses, virus tube flocculation, gel diffusion precipitation, fluorescent antibody technique, hemadsorption and immune-adherence as well as many well selected references.

The ophthalmologist is well aware of the increasing frequency of viral diseases, particularly herpes simplex keratitis, in the patients who receive steroid and antibiotic therapy. He is also well aware that, in all probability, much of his future anti-infectious therapy will be based on the knowledge of viral ocular diseases. It is essential for him to keep abreast of the advances made in this field and this present issue of the British Medical Bulletin devoted to current virus research will provide an excellent source of information and will help to bring him up to date.

IRVING H. LEOPOLD

Services to Blind Children in New York State, by WILLIAM M. CRUICKSHANK, PH.D. AND MATTHEW J. TRIPPE, PH.D. 495 pp., 17 figs., 219 tables, and photographs. $5.00. Syracuse University Press, Syracuse, N. Y., 1959.

A 2-year study of the degree to which the state of New York meets its responsibility for the education and welfare of its blind children and youth was begun in 1956. It is, without question, the most extensive examination of the problem which has been undertaken in any state. In 1956, the blind under age 21 in the United States numbered 30,200. Blind children must have an educational program equal to the best available to the sighted so that well adjusted blind adults may evolve who will be vocationally successful in terms of their potentials. The authors, Prof. Cruickshank and Dr. Trippe, are respectively the director of education for exceptional children and the director of research in special education and rehabilitation at Syracuse University.

The oldest American schools for the blind, the Perkins Institution in Massachusetts and the New York Institute for the Education of the Blind, founded in

1831, still function as educational centers. They initiated the primary pattern of blind schools throughout the country. In 1900, Chicago established the first public school class for the blind, an innovation soon followed by other cities. Various plans are now used—the residential school, the special class in the local public school and the integrated program. In the integrated program supplemental services must be available; and mobility training and braille instruction should be provided. Teachers who work with both blind and semisighted must understand the educational techniques appropriate for both. The characteristics of the individual child and his family should determine the educational plan selected.

In 1956 the state of New York had 2773 blind under age 21. Three-quarters of this number experienced the onset of blindness before age 5. The largest number of blind children (1520) were included in ages 6 to 10. A consistently higher incidence of blindness among males is found in all age groups—55 *versus* 45 per cent. Of the blind children of school age, 43 per cent are in residential schools, 26 per cent in public schools and 31 per cent are not in school. Half the number need a personal guide in unfamiliar surroundings. More than one-third attending integrated classes have a visual acuity of 20/200. In the residential schools nearly three-fourths have less that 5/200 acuity.

Multihandicapped children constitute an important segment of the total population of blind youth. In Illinois the assistant director of education for exceptional children is responsible for their educational program. In addition to blindness 31 per cent have one or more disabilities including speech impairment (28 per cent), emotional instability (28 per cent), retarded mental development (20 per cent) and cerebral palsy, epilepsy, heart disease and glandular disorders. The establishment of centers for blind, mentally retarded children is urgently needed.

Services must be rendered the blind child as promptly as possible so that both the family and the child can adjust properly. Preschool service and parent counseling must be brought to the family when the family is emotionally unable to seek the services themselves. At present a significant lag ensues between the onset of blindness and the provision of services. Compulsory reporting is not as effective as other and more acceptable ways of case finding.

An effective liason between the rehabilitation service and the schools is essential. The vocational problem in the adolescent blind is considerably different from that in the blind adult.

This elaborate analysis of the services available to blind minors will be helpful throughout the Union in planning for the better education and rehabilitation of this group.

JAMES E. LEBENSOHN

Hope Deferred. Public Welfare and the Blind, by JACOBUS TEN BROEK, PH.D. AND FLOYD W. MATSON. 272 pp., index. $5.00. University of California Press, Berkeley, Calif., 1959.

The problem of creating equality of opportunity for the blind depends, first of all, on erasing public prejudice and the discrimination to which it gives rise. The

authors emphasize the similarity between the minority status of the blind and that of ethnic and religious subgroups and suggest that the solutions found to problems of prejudice in general may be equally applicable in dealing with their handicap. The prospects for America's 350,000 sightless citizens to achieve social integration and unhampered economic opportunity are a still a hope deferred. The blind as a group have a need for shelter but not to be sheltered, a need for adjustment but not for patronage. The blind are helped in distress but not out of it. Despite a dramatic record of progress the goal of integration is far from realized.

Prof. ten Broek, a possessor of several degrees in law, traces in meticulous detail the legal progress from the Elizabethan poor laws to the present federal-state participation in public assistance, social security, medical care and rehabilitation. It took two world wars to establish the existing rehabilitation services. Though these vary from state to state, they are uniformly inadequate to meet the needs of the sightless. Where relief and rehabilitation are administered by the same agency the blind are often viewed as totally incapacitated and fit only for case relief or sheltered workshops. Consequently the organizations of the blind, such as the National Federation of the Blind, are demanding the establishment of independent rehabilitation bureaus apart from state welfare agencies.

Sighted counselors underestimate the abilities of the blind and tend to guide the sightless into stereotyped occupations. Those who can most fully judge the true effect of blindness and thereby serve most competently in the guidance of the newly blinded are other blind persons. In view of their virtually indispensable role in guidance and counseling, the training of qualified blind persons for positions within the rehabilitation program should be extensively encouraged.

Vocational training has a definite therapeutic value in freeing the individual from his initial helplessness and giving him a sense of productivity and achievement. To seek less than full vocational rehabilitation is to deny the blind the right of equal opportunity and personal independence. For those capable of full restoration and productive employment the sheltered workshop is a blind alley.

Prof. ten Broek is a member of the President's Committee on Employment of the Physically Handicapped and has been associated with the California State Board of Social Welfare. The message of the book is unusually well expressed as both authors are in the Department of Speech at the University of California.

JAMES E. LEBENSOHN

Roentgenologic Diagnosis in Ophthalmology, EDWARD HARTMANN, M.D. AND EVELYN GILLES, M.D. $15.00. J. B. Lippincott Company, Philadelphia, 1959.

This book makes available to the ophthalmologist advances in the field of roentgenology and to the roentgenologist the apparatus and techniques most important to the ophthalmologist. It represents the combined efforts of an ophthalmologist and a roentgenologist. The text was originally written in French and has been translated by George Z. Carter for the English-reading ophthalmologists and roentgenologists. The editing of the translation was done by Conrad Berens.

The 365-page text discusses in 13 chapters the roentgenologic technique for studying the walls of the orbit optic canal, the superior and inferior orbital fissures, fractures and tumors of the orbit, the eyeball, localization of intraocular foreign bodies, lacrimal pathways, paranasal sinuses, dental infections, the apex of the petrous bone, the sella turcica, study of the cranial vault, arteriography, ventriculography, encephalography, cisternography, phlebography, and lesions of the cervical spine. Each chapter is covered by adequate references at the end of the text.

The illustrations are excellent, and one cannot help being impressed with the manifold contributions of roentgenology to the ophthalmologist in diagnosis. Considerable amount of neuro-ophthalmology is dealt with in this text. There is no doubt that study of this text would be greatly aided by simultaneous study of the actual roentgenograms as patients are studied in the individual institutions by the ophthalmologist. Ideally, the text should be read as patients present themselves with the problems covered in the book and the roentgenograms should be studied in the roentgenologist's film reading room. Busy ophthalmologists have a tendency to depend simply on the written report of the expert roentgenologist. This text points out the advantages of close and direct association between the two specialists.

The roentgenologic examination of exophthalmus is carefully considered. A very helpful differential diagnostic table is available.

There are very few ophthalmologists who are well versed in roentgenology. The senior author of this text has been interested in this subject for at least 30 years and actually produced an Atlas of Clinical Radiography in Ophthalmology in April 1936. The present text is in no way related to the earlier one. The present text's principal object is to be practical and to serve as a reference for the roentgenologist or ophthalmologist who may have difficulty in solving a problem encompassing these two specialties. The authors, both highly respected authorities in their fields, have collaborated to produce a detailed book which covers the intended subject with due consideration to the latest developments.

IRVING H. LEOPOLD

Current Review

UVEITIS—A REVIEW

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Classification

The most notable advance in classifying uveitis occurred in 1947 when Woods,[206] guided by the histopathologic characteristics of enucleated eyes, subdivided uveitis into two varieties: the nongranulomatous and the granulomatous forms. Presumably the former represented a reaction of hypersensitivity, and the latter resulted from actual organismal invasion. According to Woods these two types of uveal inflammation are entirely dissimilar in clinical appearance, pathogenesis, and microscopic alteration.

However, in recent years the exact validity of this classification has been questioned on both clinical and pathologic grounds.

Clinically, the differentiation between the two types is not always sharp. The granulomatous changes with thick lardaceous keratic precipitates and marked fibrin formation are also seen frequently in anterior uveitis presumably of the sterile allergic variety, whereas in chronic anterior uveitis the same indolent reaction seen in the granulomatous type of uveitis often occurs. Clinically, at least, it would appear that the same manifestations may be produced at different times by either the allergic reaction of the nongranulomatous form, or the so-called proliferative reaction which presumably results from organismal invasion in granulomatous uveitis. In fact, it would seem that in some instances the only difference between the two varieties can be said to be one of degree due to the severity of the reaction rather than to the type or nature of the causative mechanism.

In this connection it is interesting to note that in leptospiral uveitis, where actual tissue invasion occurs, the reaction is considered by many[162, 187] to be of the nongranulomatous variety. Clinically, the differences between the two types are not always clear-cut and both processes may overlap so as to render certain differentiation between them impossible. Woods himself[208] calls attention to this point—especially in the more chronic forms of the disease. Certainly endophthalmitis phacoanaphylactica, which is considered to be a disease of hypersensitivity, presents a typical granulomatous appearance on slit-lamp examination, yet no organismal infiltration occurs in this disease.

Ashton[5] and others[157, 184b] have indicated that pathologically the terms granulomatous and nongranulomatous are without any real meaning. In the past, pathologists utilized these terms to describe the proliferative and chronic reactions which characterize syphilis, tuberculosis and leprosy. This usage has become obsolete since these reactions are now regarded as examples of chronic inflammation, manifesting histologic features which are to be found in almost any chronic inflammation. Ashton points out that practically any inert irritant, such as talc, beryllium, wood or silica is capable of producing similar proliferative granulomatous responses.

Rich[157] has stated that the term "granulomatous inflammation" lacks specific meaning, since it can occur in purely immunologic processes as well as in lesions in which immunology plays no role. He has created "beautiful tuberculoid reactions" in the absence of infection by using sterile, nonbacterial antigens and antibodies alone.

Goldgraber and Krisner[68] have indicated that the granulomatous state, with or without giant cells, is highly characteristic of the hypersensitive state in the experimental animal. They feel that the presence of granulomas should arouse suspicion of a hypersensitive state. This work is at variance with Woods'[208] findings.

Frenkel and Jacobs[65] state that the so-called "granulomatous" character of the eye lesion in toxoplasmosis is nonspecific and that it is not pathognomonic for toxoplasmosis. According to them it probably results from a reaction to pigment. They state that this reaction is not found in any other tissue lesion, nor is it seen in animals afflicted with toxoplasmosis.

Thus it would appear that terminology in uveitis is still in need of further definition. Classification based upon etiology is impossible as yet, since more often than not the etiology cannot be determined satisfactorily. Classification based upon histopathology is not satisfactory for the reasons mentioned, and furthermore, it is difficult to correlate histopathology with clinical manifestations.

In our present state of knowledge the purely descriptive anatomical terms—anterior, posterior and panuveitis—though inadequate, may be preferred to attempts at more precise classification which tend to imply more knowledge than is presently available. In the Uveitis Clinic at the New York University-Bellevue Medical Center, all uveitis is classified anatomically and, whenever possible, a supplementary morphologic description of nongranulomatous and granulomatous is given.

Pathogenesis

Focal Infection

It is only in the field of ophthalmology that one still finds adherents to the hypothesis of focal infection, which, in the light of present day knowledge, is more acceptable if considered as an antigenic focus rather than an infectious one. Utilizing the concept of an antigenic focus, several authors[2, 3, 77, 111, 135, 208] contend that instances of uveitis are due to foci of infection and that eradication of foci results in cure of the uveitis. Holland and Worlton[86] have emphasized the importance of the pleuropneumonia-like organisms (PPLO) found in the genital tract as a cause of uveitis. They reported that in five patients systemic chemotherapy resulted in clinical improvement of the uveitis coincident with eradication of the organisms in the genitourinary tract.

Examining 150 patients with uveitis, Catterall[25] found evidence of a chronic prostatovesiculitis in 88.5 per cent of 105 patients with anterior uveitis. However, he was unable to demonstrate any causal relationship between their ocular and genital diseases and the PPLO organisms. In this study, extensive bacteriologic investigations and serologic testing failed to reveal a likely causative organism However, he considered the genital infection to be a common factor in patients with anterior uveitis, Reiter's disease and ankylosing spondylitis.

Offret and Sarraux[135] estimate that focal infection accounts for 35 per cent of all uveitis. They report[133] the successful isolation of the same organism from the aqueous and from foci of infection. However, they underline the difficulty in

making a diagnosis with any certainty because of the possible multiplicity of foci of infection and the many instances of cross allergies which exist in these patients. They advised caution before making a definite diagnosis of uveitis due to focal infection.

Many investigators,[9, 168, 179, 184a, 185] including the author, have not been impressed with the results of the information gathered from surveys for foci infection as a cause of uveitis. While instances of the cure of uveitis following the extirpation of such foci do occur, this is more the exception than the rule.

Direct Organismal Invasion

Bacteria

The absence of bacteria in the aqueous during attacks of iridocyclitis seems to be well established in this country.[193, 208] However, in Europe, where diagnostic aqueous aspirations seem to be performed more frequently, the literature abounds with reports demonstrating the recovery of bacteria from the anterior segment during the course of uveitis. Verrey[191a, 191] pioneered this approach in the study of uveitis and reports the recovery of organisms from the aqueous in about 4 to 8 per cent of his patients. This work has been duplicated in recent years by Offret and Sarraux,[135] who reported isolation of streptococci and staphylococci in 15 per cent of their patients. In a few instances they were able to cultivate the organism—although in most instances they were nonspecific bacteria which exhibited little or no virulence. Kapuscinski[98, 100] has also reported the recovery of bacteria from the aqueous—mainly staphylococci. It was also his impression that the staphylococci isolated from the conjunctival sac were of great importance. Remky and others[155, 156 135] have also reported the isolation of various bacteria from the aqueous during the course of uveitic inflammations.

On the other hand, Preisova[152] recovered staphylococci from the aqueous in 100 normal subjects. This observation tends to support our impression that the bacteria which have been isolated from the aqueous in the presence of uveitis most commonly represent contaminants from the conjunctival sac. We are in agreement with Woods[208] who has referred to these organisms as nonpathogenic and as either conjunctival contaminants, or "dead on arrival" in the anterior chamber. If these bacteria bear any relationship to uveitis it would be expected that the administration of antibiotics would lead to recovery in some instances. However, antibiotics are of little or no aid in managing nonspecific uveitis. Furthermore, staphylococci, streptococci and pneumococci elicit purulent reactions, and their presence in the ocular tissues invariably leads to endophthalmitis or panophthalmitis—not an iridocyclitis.

The mycobacterium tuberculosis has been recovered from the eye and is an accepted cause of uveitis. It will be discussed in detail later.

Toxoplasmosis

Since Jacobs, Fair, and Bickerton[90] presented the first parasitologically proved instance of adult toxoplasmic uveitis, three reports of the recovery of live *Toxoplasma gondii* in human eyes have been published.[73, 84, 149] All recoveries were

TABLE 1

Recovery of Toxoplasma from Human Eyes

Author	Sex and Age	Duration	Type	Ant. vs. Post.	Eye Involved	Skull X-ray	Dye Titer		Virulence
							Before	After	
Jacobs, L., Fair, J., Bickerton, J., 1954[80]	Male, 30 yrs.	8½ yrs.	Acquired	Post.	O.S.	Neg.	1:64	1 wk. 1:4096 2 wks. 1:128	High
Habegger, 1954[73]	Male, 2 mos.	Since birth	Congenital	Post.	O.D.	Hydrocephalic	1:6000		?
	Female, 45 yrs.	?	Congenital	Post.	O.D.—new O.S.—old	Neg.	1:2048	1:16000	High
Hogan, M. J., Zweigart, P., Lewis, A., 1958[84]	Male, 20 yrs.	8 yrs.	Congenital	Post.	O.D.—old healed central C.R. O.S.—Active lesion	Pos.	1:128	1:16	Low
Pillat, Thalhammer, 1957[149]	Male, 11 yrs.	3 mos. (?)	?	Ant.	O.U.	?	1:16384	1:256	?

from the posterior segment of the eye with the exception of the report by Pillat and Thalhammer, where the recovery occurred in an eye with recurrent iridocyclitis.[149] However, it is not clear from the report whether the iris and retina were separated prior to animal inoculation. Table 1 lists the clinical features in those instances in which the Toxoplasma was recovered from human eyes. Several reports of the pathologic identification of Toxoplasma in excised human eyes have appeared.[50, 197, 218]

VIRUSES

Viral uveitis is not uncommon, although no virus has been demonstrated which sossesses an elective tropism for the uveal tract. Most viral uveitis is usually pecondary to systemic viral disease or to local virus infection of the eye or its adnexa.

Isolation of viruses from the anterior chamber in the course of uveitis has been recorded occasionally in the literature,[27, 89, 151] although most investigators[189] have been unsuccessful in isolating viruses during the course of suspected viral uveitis. Since viruses are known to be intracellular parasites, possibly the failure can be ascribed to the technique wherein only aqueous is aspirated. However, Thygeson, Kimura and Hogan[189] have found that herpes virus injected intracamerally in rabbits does not thrive and cannot be recovered from the eye 4 days later. The experimental production of viral uveitis by these investigators has proved to be unrewarding. In a later section the clinical manifestations of viral uveitides will be discussed.

The following well recognized clinical uveitides are believed to have a viral etiology although the evidence in some instances appears tenuous.

Behçet's Disease

Rather uncommon in this country, Behçet's disease has been reported upon extensively in the European literature. It is generally agreed that the etiologic agent is a virus. Ocular recovery of the virus from the subretinal fluid, as well as the presence of neutralizing antibodies in patients with this disease, has been reported by Evans *et al.*[55] and Sezer.[175b,c]

Sympathetic Ophthalmia

Etiologic theories abound; almost all may be classified as either infectious or allergic. The oldest is the infectious theory, which assumes that a bacteria, virus, or a rickettsial-like organism, present as a saprophyte on the conjunctiva or cornea becomes pathogenic upon contact with uveal tissue.

Recently, a new etiologic concept involving both the infectious and the uveal allergy points of view has been proposed by Ikui and associates.[88, 89] With the electron microscope they observed what seemed to be virus-like particles in and around inclusion bodies. These particles had an inner core of low electron density measuring 40 to 75 mμ surrounded by a shell of high electron density of approximately 25 mμ. In addition, they observed basophilic globular inclusions in some epithelioid cells along with some scanty pigment granules. It is the authors' impression that the epithelioid cells are former chromatophores which have been modified by the virus-like particles identified under the electron microscope. It is their belief that a virus exists which possesses a specific trophism for certain types of pigment cells in the uveal tract.

Utilizing this concept they postulated that a virus, by combining with uveal pigment, could result in this altered uveal tissue acting as an antigen to produce a state of hypersensitivity in normal uveal tissue. Obviously, the virus would possess a specific trophism for uveal pigment.

Sery[174] has aptly described the objections to the virus theory in the pathogenesis of sympathetic ophthalmia by pointing out that it is unlikely that a single virus could be associated with the many disparate objects involved in ocular trauma. If the virus is instead associated with the ocular tissues, why is it so infrequent despite surgical intervention and penetrating wounds which occur so commonly? Perhaps it is because the virus: (*a*) is not present in many eyes; (*b*) is present in low concentration; (*c*) requires some unknown activating agent; (*d*) is present only at certain times in some eyes, such as if carried there by droplet infection.

Most damaging to the infectious theory in the causation of sympathetic ophthalmia has been the failure to discover any organism with any regularity in eyes with sympathetic ophthalmia. The organisms reported by some observers have not been found by others. This is all the more unusual in terms of the various *in vitro* and *in vivo* methods of cultivating viruses, pleuropueumonia-like organisms, rickettsia and bacteria which are available. Inoculation experiments have failed to reproduce the disease. To us an allergic pathogenesis seems more tenable.

Vogt-Koyanagi-Harada Syndromes

These syndromes are believed by some[60, 74, 154, 215, 216] to be different aspects of the same disease which has been classified as the uveomeningeal group. Several investigators[215, 216] have implicated a viral causation. Yoshida[215] claims to have successfully isolated a virus from a patient with uveomeningitis which maintained its ability to incite uveitis after 18 transfers on allantoic material. Investigators in this country have been unsuccessful in their attempts to isolate a virus.[189]

RICKETTSIA

Thomas[188] has recently called attention to rickettsia as a cause of uveitis and reports four instances of rickettsial uveitis where the ocular involvement was the sole manifestation of the disease.

Schreck[173] has postulated that sympathetic ophthalmia is due to a rickettsial-like organism.

SPIROCHETOSIS

Leptospirosis

Recovery of live leptospira from human eyes has been reported[1] as well as the pathologic identification of the causative spirochete in enucleated eyes.[162]

Syphilis

This organism has been recovered from human eyes on many occasions.

PARASITIC DISEASES

Ocular recovery of live nematodes from human eyes has been reported fairly frequently[18, 23, 161] and, although encountered relatively rarely in the United States, ocular parasitic infection is common in the tropics.

FUNGUS INFECTIONS

The cultural or histologic identification of fungi in eyes with endogenous uveitis has been reported frequently enough[208] to leave little doubt that infection with fungi may be a cause of granulomatous uveitis. Actinomycosis, blastomycosis, Cryptococcus and Aspergillus have all been isolated from human eyes. Woods[208] is of the opinion that the histoplasma capsulatum may well play an important role in the causation of granulomatous uveitis, although it has not yet been isolated from human eyes.

Hypersensitivity

At the present time an allergic mechanism is believed primarily responsible not only for the obviously allergic reaction of the uvea occurring during serum sickness, angioneurotic edema, and other immediate forms of allergy, but also for the inflammatory processes characteristic of the rather common nongranulomatous, sterile forms of endogenous uveal inflammation. This delayed allergic reaction is believed to be of the microbial type. Another form of allergic response

TABLE 2
Allergy of the Uvea

1. Anaphylactic and atopic reactions:
   Uveitis from sera, pollens, animal proteins, foods, drugs, angioneurotic edema
2. Microbiallergic reactions:
   a. Nongranulomatous uveitis (allergy apparently the main factor): Streptococcus, tubercle bacillus, Staphylococcus, Gonococcus, Pneumococcus
   b. Granulomatous uveitis (allergy not primary factor but may alter the nature of the inflammatory response): tuberculosis, syphilis, toxoplasmosis, brucellosis
3. Autogenous allergic reactions:
   a. Sympathetic ophthalmia (allergy to autogenous uveal pigment)
   b. Endophthalmitis phacoanaphylactica (allergy to autogenous lens protein)

to autogenous allergy also appears to operate in the causation of sympathetic ophthalmia and in phacotoxic uveitis.

Coles and Theodore[35] have offered a useful clinical classification of uveal hypersensitivity (Table 2), which embraces practically all aspects of uveitis and assumes that allergic reactions are of the two major types: (1) the immediate form (anaphylactic and atopic varieties), and (2) the delayed form (tuberculin type). The latter type may result from various autogenous allergens as well as from microbial products. With the latter type of reaction they employ the term "microbiallergic."

ANAPHYLACTIC AND ATOPIC REACTIONS OF THE UVEA

While rare, these offer the best clinical corroboration of the fact that the uvea may participate in generalized allergic reaction as in serum sickness.[35] Other instances of atopic or allergic uveitis may result from hypersensitivity to inhalants and foods, as has been shown in a previous review.[35]

MICROBIALLERGIC REACTIONS OF THE UVEA

At present it is believed by some that bacterial allergy originating from a distant antigenic focus is the major mechanism in endogenous nongranulomatous uveitis. Organisms inciting apparently definite allergic reactions of this type would include Gonococcus, Streptococcus, Staphylococcus, Pseudomona, coliform organisms, and Pneumococcus. The tubercle bacillus and other organisms causing granulomatous infections may induce superimposed hypersensitivity reactions. Clearly proved instances of microbiallergic endogenous uveitis are, however, rare.

Streptococcal Uveitis

In recent years it has been accepted by some[2, 3, 155, 208] that most instances of anterior nongranulomatous uveitis are examples of delayed bacterial (tuberculin type) reactions to the streptococcus—a microbial reaction—emanating from a distant antigenic focus.

EVIDENCE FOR STREPTOCOCCAL ALLERGY. The basis for implicating the Streptococcus rests upon the following evidence:

Antistreptolysin-O Titer (ASLO). Several investigators[114, 172, 182, 204] have reported finding higher average ASLO titers in the serum of patients with acute anterior uveitis than in patients with posterior uveitis or in a control group. Recently, Laffers and Bozsoky[107] have reported finding ASLO in the aqueous of patients with uveitis which they feel indicates a streptococcal etiology. Remky[155] also found aqueous ASLO titers to be higher than serum titers in patients with anterior uveitis. He regards this as evidence of local antibody formation in the ocular structures and believes that this is indicative of a streptococcal etiology. He feels that one out of every two instances of anterior uveitis is streptococcal in origin. Witmer believes that ASLO determinations are far more satisfactory than swabs and cultures of suspected foci in arriving at a diagnosis of streptococcal uveitis.[204]

Skin Testing. Woods[208, 209a, 209b] demonstrated by intradermal skin testing that 89 per cent of patients with nongranulomatous uveitis exhibited a specific hypersensitivity to various strains of streptococci, whereas in a control group only 20 per cent reacted positively. Others[2, 3, 77] have reported similar findings.

Correlation Between Aqueous Findings and Foci of Infections. Offret and Clop[136] report the isolation of a Streptococcus from the aqueous and remote foci of infection which possessed identical characteristics. They regard the streptococci as a prime cause of uveitis and feel that streptococcal uveitis is frequently related to infected tonsils. Legrand and Baron[111] share this opinion.

Desensitization. Patients with anterior uveitis exhibiting hypersensitivity to specific streptococci were desensitized by Woods,[208, 209a, b] who found that in many there were no subsequent attacks and that in others the frequency and severity of the attacks diminished.

EVIDENCE AGAINST THE STREPTOCOCCAL ALLERGY THEORY. Coles and Nathaniel[34, 37] however, have questioned the association of the streptococci with anterior nongranulomatous uveitis and have summarized their objections:

Antistreptolysin-O Titer. In their studies they were unable to find any correlation between serum ASLO titers and either anterior or posterior uveitis, thus confirming the work of other investigators in this respect.[10, 75, 192]

With reference to the finding of elevated aqueous ASLO titers, Sery[184] and Leopold[115a] have pointed out the prevalence of serum ASLO in a large segment of the normal population, and have indicated that the disturbed blood-aqueous barrier present in uveitis might account for the presence of ALSO in the aqueous.

Skin Testing. The results of skin tests should be interpreted with caution, since nonspecific reactions may occur. Furthermore, whereas skin tests may indicate a general state of hypersensitivity, this is not necessarily related specifically to any one particular organ, such as the eye. Also, since streptococci possess a complex antigenic mosaic with many somatic antigens and exotoxins capable of producing antibodies, misinterpretations may arise on this basis alone.[176]

Variations in the techniques of administering skin tests, and differences in the methods of preparing the same test antigen, often yield conflicting results, as was shown in a recent study by Perlman.[148] With the use of, theoretically, the same antigen prepared by 5 different commercial houses on the same test subjects, he

obtained reactions which varied from strongly positive to negative. The clinical significance of streptococcal skin reactions is often doubtful. Thus, Lawrence[110] found positive skin reactions to streptococcal fractions in a large segment of a random hospital population. His study indicated that in a group of 472 patients, 88 per cent exhibited positive reaction to streptococcal material, a figure quite similar to that found by Woods[209a, b] in his patients with nongranulomatous uveitis.

Foci of Infection and the Streptococcus. This phase of the problem has been discussed above. Here we would merely wish to reiterate the work of Stanworth,[184a, b] who found little correlation between cultures for streptococci and foci of infection and uveitis.

Desensitization. Desensitization therapy is almost impossible to evaluate in a disease as capricious as uveitis with its spontaneous exacerbations and remissions. Some investigators feel that Woods' results with this therapy are indistinguishable from events noted without therapy during the natural course of the disease.[80a]

However, one cannot eliminate the possibility that therapeutic amelioration following desensitization with streptococcal vaccines may be due to some nonspecific factor present in the vaccine. Woods[209] himself has mentioned this possibility.

Recently, Levine and Breinin[116] have added further support to this possibility in their observations on endotoxin uveitis. Endotoxin is a lipopolysaccaride-protein complex which is present in the intact cell of a wide variety of Gram-negative microorganisms, and is the active pyrogen in all agents employed for fever therapy. They point out that Stetson has demonstrated that hemolysates of hemolytic streptococci contain endotoxin.

The ability of endotoxin to cause iritis in experimental animals has been reported, and it is also known that subjects can be rendered tolerant to endotoxin by intravenous administration in graduated amounts.[116] Levine and Breinin have postulated that the clinical improvement resulting from streptococcal desensitization is due possibly to the nonspecific effect of the endotoxin present in the vaccine but not peculiar to the Streptococcus. If this is so, it would be consistent with our own experimental findings that the Streptococcus may not be an important factor in the causation of uveitis.[34, 37]

It is of some interest also that streptococcal uveitis is rare in young persons under the age of 16, where known streptococcal diseases such as rheumatic fever and glomerulonephritis are more common than after this age. But only 5 per cent of uveitis[182]—and that predominantly the posterior variety[181]—occurs below the age of 16.

It would seem to us that there is little correlation between streptococcal disease and anterior uveitis. The justification for treating patients with intravenous streptococcal vaccine is not yet fully established. While instances of streptococcal uveitis undoubtedly do occur, it is the opinion of this reviewer that it is a relatively rare occurrence.

Microbiallergic Reactions due to Other Bacterial Antigens

Gonococcus

The importance of chronic gonococcal infections in the causation of anterior uveitis, more commonly seen by clinicians in the recent past, has now waned with better control of venereal diseases. There is highly acceptable evidence that bacterial allergy, not direct bacterial invasion, is the inciting factor. The especial value of foreign protein therapy and hyperpyrexia is strong evidence in this regard. Gonococcal complement fixation tests while of debatable significance nevertheless are almost regularly positive in such patients and are certainly suggestive as to etiology. Gonococcal antigens induce markedly positive reactions on intradermal injections. Of course, even in this antibiotic era, any particularly severe plastic anterior uveitis should alert the ophthalmologist to the possibility of a gonococcal origin of the uveitis, especially if the history or general examination is suggestive.

Rarely, other bacteria may evoke nongranulomatous uveitis on an allergic basis. These include *Pseudomonas aeroginosa*, the pneumococcus, coliform organisms, and rarely the Staphylococcus.[33]

Tuberculosis

Tuberculosis is an excellent example of a granulomatous uveitis caused by direct bacterial invasion in which the clinical inflammatory reaction may be modified by local tissue hypersensitivity. Moreover, it is believed that at times allergy may be the sole precipitating factor and that direct infection of the uvea need not occur. Ashton,[5] for example, has focused attention on the concept that hypersensitivity reactions in the uvea can result from some extraocular form of tuberculosis. He leans to the belief that tuberculous uveitis may often occur on an allergic basis instead of being the result of direct organismal invasion. He found the tuberculin test was positive more often in acute anterior uveitis than in chronic posterior uveitis.

The ability of the uveal tract to react allergically to soluble fractions of the tubercle bacillus without actual tissue invasion or proliferation of the organism is well known. The uvea can be sensitized to circulating tubercle bacilli, living or dead, or to their soluble products. Thereafter, the eye can react allergically to circulating moieties of the bacillus. Thus it appears that anterior uveitis may occur as a manifestation of hypersensitivity to products of the tubercle bacillus in the absence of direct infection, as is known to occur in phlyctenular keratoconjunctivitis, and in scleritis. Exacerbations of uveitis following testing or therapy with tuberculin in otherwise healthy individuals is known to occur clinically.[31, 126, 127, 158, 195, 196] Moreover, it has been found[15, 153] that the destruction of tubercle bacilli by means of chemotherapy apparently liberates sufficient antigen to cause focal allergic reactions which subside when chemotherapy is stopped. This is analagous to the Herxheimer reaction.

Rich[158] has underscored the possibility that the typical tuberculoid lesion can appear merely as a result of a local antigen-antibody reaction. The pathologic

manifestations are those of a typical "granulomatous lesion" without the presence of bacteria. According to this, not only may the typical acute anterior nongranulomatous uveitis arise on the basis of an allergic response to products of the tubercle bacilli, but also a posterior, typical granulomatous variety may occur without bacterial invasion.

In those instances where uveal tract invasion by the tubercle bacillus does occur, the balance between allergy and immunity and host resistance to the infesting organism determines the nature of the clinical response and accounts for the tremendous pleomorphism of the lesion in uveal tuberculosis. This has been well described by Woods.[208]

Toxoplasmosis

Whether toxoplasmic uveitis is associated with any important degree of local tissue hypersensitivity is largely conjectural.

It has been suggested[64, 65] that the toxoplasma after localizing in the retina forms pseudocysts in the parasitized retinal cells, in which they may lie dormant for many years. Both local and general sensitization occur, the latter manifested by low positive dye titers. When, perhaps years later, because of changes in immunology, quiescent pseudocysts rupture, the sensitized tissues react with the liberated organisms and cause a marked allergic inflammatory reaction. The severity of the vitreous clouding and visual loss depends upon the degree of hypersensitivity. Sabin[164] feels that there is strong support for the concept that adult ocular toxoplasmosis may represent an allergic inflammation in response to rupture of congenital pseudocysts. Hogan,[80] however, has expressed some skepticism of this theory since no experimental confirmation is available as yet.

AUTOGENOUS UVEITIS

Autogenous uveitis provides an excellent example of the concept of autoantibodies, which is well demonstrated in autogenous uveitis due to lens protein (phacotoxic uveitis) and that due to uveal pigment (sympathetic uveitis).

Phacotoxic Uveitis

Several excellent reports covering clinical, theoretical and experimental aspects of phacotoxic uveitis have appeared in the past year.[28, 203, 211] While phacotoxic uveitis appears clinically to be a definite allergic reaction, the fact that its experimental production in animals has required adjuvants has led some investigators to believe that the mechanism is a direct toxic effect rather than allergy.

The evidence for and against the hypersensitivity pathogenesis *versus* the toxic pathogenesis has recently been summarized by Woods,[211] who favors the former hypothesis. He believes that the question cannot be answered conclusively until a specific antigen-antibody reaction to the α-crystalline (the organ specific constituent of lens protein) present in the eyes of patients with this disease can be demonstrated.

Witmer[203] believes that phacotoxic uveitis can represent either a toxic or a

hypersensitive reaction to lens protein. He postulates that a low grade subclinical infection—exogenous or endogenous—is present which makes the lens antigenic. This concept calls to mind Burky's[20] experimental work on phacotoxic uveitis. Burky succeeded in reproducing the pathologic picture of endophthalmitis anaphylactica in rabbits by first sensitizing them to Staphylococcus toxin and lens substance. When cutaneous sensitivity had been established, by needling the lenses in these animals he succeeded in producing pathologic changes in the operated eye which resembled phacotoxic uveitis. Burky felt that his experiments indicated an allergic pathogenesis. Lyda *et al.*[119] have recently duplicated much of this work.

Witmer[203] has developed a serologic test which determines the antibody titer in the aqueous against its own lens.

What is perplexing about this entity is the fact that some people tolerate free lens material in the aqueous with no undue reaction while other patients develop an acute inflammation. It could well be that some other factor—perhaps low grade infection—must be present to act as an adjuvant that triggers the disease. Systematic skin testing with lens protein may prove to be of value in determining the actual role that hypersensitivity plays in phacotoxic uveitis.

Sympathetic Ophthalmia

Analysis of what is known, experimentally and clinically, concerning sympathetic ophthalmia, leads to the conclusion that the most acceptable pathogenesis of this entity is some form of hypersensitivity. Uveal pigment seems to be the basic exciting antigen as first shown by Elschnig[53] in 1910. Woods demonstrated a specific antibody to uveal pigment in humans following perforating ocular wounds, demonstrable on intradermal skin-testing.[205]

Friedenwald,[66] utilizing histologic studies on the skin of individuals who had received such intradermal injections of suspensions of uveal pigment, felt that the uveal pigment granules acted as a specific antigen and that the disease was primarily allergic in nature.

Contralateral uveitis simulating sympathetic ophthalmia has been successfully reproduced in experimental animals following sensitization of one eye. This type of reaction is referred to as "elective sensitization," and has been attributed by some[62] to excess antigen escaping via the bloodstream to the fellow eye at the time of initial sensitization. Others[169] hold that the reaction is due to circulating antibody which reacts with the antigen of the contralateral eye.

Österlind[139, 140] has demonstrated that elective sensitization is entirely dependent upon the active participation of the uveal tissue of the first eye. Having standardized his sensitization technique to a point where he could reliably expect elective sensitization in 50 per cent of the untreated eyes he discovered that the reaction failed to occur if: (*a*) the sensitized eye was enucleated during the first two weeks, and (*b*) if the uveal tract was destroyed by too severe a reaction, or by a purulent reaction. This brings to mind the "laudable pus" which veterinarians introduced into a horse's traumatized eye to prevent the "infection" from spreading to the fellow eye.

Friedenwald[66] has reported a case of sympathetic ophthalmia which healed spontaneously; microscopic examination revealed that the choroid had been replaced by scar tissue and that there was no remaining pigment. Also, the 2-week grace period which Österlind found corresponds quite accurately to the earliest recorded appearance of sympathetic ophthalmia in humans following trauma. These experiments emphatically indicate the importance of the uveal tract in elective sensitization.

However, it must be pointed out that the contralateral reaction in the rabbit eye, while undoubtedly a reaction of hypersensitivity, most certainly fails to present the pathological picture of sympathetic ophthalmia. Schmedtje[171] has pointed out that the inflammation in the second eye consists of a moderate round cell infiltration usually followed by complete recovery; and that the time sequence in the animal is usually 1 to 2 weeks whereas sympathetic ophthalmia may occur after an interval of many months. He found that he could abolish elective sensitization by sympathetic denervation of the contralateral eye, which he believes interrupts the reflex pathways responsible for this contralateral reaction. He finds little support in his work for a humoral mechanism.

Nonetheless, it would seem that hypersensitivity to uveal pigment is the basis of the reaction leading to sympathetic ophthalmia. That this reaction is more complicated and requires special circumstances for its development is suggested by recent work. Collins[38, 39] for example, succeeded in producing lesions in the choroid of guinea pigs which histologically simulated the picture of sympathetic ophthalmia. However, he found that it was necessary to employ Freund's adjuvant (heat-killed tubercles in mineral oil) in addition to the uveal pigment to get the typical picture of sympathetic ophthalmia in these animals. Interestingly, however, when he ascended the phylogenetic tree and repeated these same experiments in monkeys he could only produce a much milder disease. Unfortunately, his work has not been duplicated as yet.

Blodi[13] recently analyzed a total of 170 eyes with sympathetic ophthalmia and found that 39, or nearly 23 per cent, showed evidence of a phacoanaphylactic reaction. He felt that this association was higher than could be expected by chance coincidence and that their simultaneous occurrence lent additional weight to the concept of an allergic pathogenesis in sympathetic uveitis.

The favorable response of sympathetic ophthalmia to steroid therapy is further indirect evidence that this is a reaction of hypersensitivity. It seems highly improbable that an infectious process would respond to the long term steroid administration that is frequently necessary to control this disease.

While there is no doubt that hypersensitivity to uveal pigment does occur, it seems clear that some other factor is necessary to trigger the reaction, either before or after uveal hypersensitivity has been established. This could conceivably include some participation of nonpathogenic conjuctival bacteria acting as adjuvants. This would perhaps tie in with the work of Streiff and Miescher[186] who demonstrated that virus infections can be considerably enhanced by previous uveal sensitization.

The similarity of sympathetic ophthalmia to Vogt-Koyanagi's disease and to

Harada's disease has prompted several authors[60, 150, 215, 216] to postulate that they are all manifestations of a single disease entity. Hager[74] and Yoshida[215] (see above) are of the opinion that a virus is the responsible agent. However, it must be pointed out that the involved structures in this disease are those which contain pigment, and it can also be postulated, therefore, that hypersensitivity to uveal pigment is the responsible factor. Until some accurate way of reproducing these disease entities in animals is discovered, no convincing proof of a viral or a hypersensitivity (or both) etiology will be forthcoming.

Heterochromic Cyclitis of Fuchs

According to Kimura, Hogan and Thygeson,[104] Fuchs' syndrome of heterochromic cyclitis occurred in 4 per cent of 1500 patients with uveitis whom they studied.

Clinically, the disease usually appears in the third or fourth decade, although exceptions in both directions have been reported. Onset is insidious, with very low grade flare and cells, a white eye, and the absence of gross inflammatory signs. Occasionally, keratic precipitates will appear on the pupillary area or on the lower cornea. These are small and white, never confluent, and fine fibrin filaments may run between them.[63] Dust-like floaters are present in the anterior vitreous. Posterior synechiae never form.

The heterochromia may be slight or marked, is more common in blue irides, increases very slowly, and involves the pigment layer which develops a moth-eaten appearance. The hypochromic eye is the affected eye, although occasionally it may be bilateral.[63]

Secondary cataracts appear late in the disease in about 15 per cent[104] of patients and are of the complicated type appearing in the posterior subcapsular area. Secondary glaucoma, which may appear late in the course of the disease, usually occurs in eyes with cataracts. It is not common.

Since the introduction of contact lens examination of the fundus and indirect ophthalmoscopy with scleral depression, peripheral choroiditis frequently has been noted to be present.

The etiology of this condition is obscure and it is thought by Woods[211] that heterochromic cyclitis represents only an unimportant late development in a chronic nonspecific low-grade uveitis, and that pathologically there is nothing distinctive about this syndrome. He does not accept it as a specific entity.

For some time a neurogenic theory of etiology was popular, the concept being that paresis of the cervical sympathetic nerve supply occurred. Perkins,[143] in a series of ingenious experiments, demonstrated that there is little support for the neurogenic theory in the causation of heterochromic cyclitis and feels that a diagnosis of heterochromic uveitis should not preclude a search for other etiologic agents.

Systemic Diseases Associated with Uveitis

In any search for etiologic agents in the causation of uveitis it soon becomes apparent that many instances of uveitis are associated with systemic diseases.

It is the purpose of this section to discuss briefly the various systemic diseases and their uveitic manifestations.

Rheumatic Diseases

Under the term rheumatic diseases are included only inflammatory changes involving the joint tissues. This classification comprises: rheumatoid arthritis, juvenile rheumatoid arthritis (Still's disease), ankylosing spondylitis (Marie-Strumpell's disease), gonococcal and gouty arthritis, Reiter's disease and rheumatic fever. Osteoarthritis and other degenerative processes are excluded from this list since these conditions are unassociated with uveal disease.[14, 112, 181, 185]

Rheumatoid Arthritis

Surveys of the literature indicate that approximately 2 to 5 per cent of patients with rheumatoid arthritis develop anterior uveitis.[83, 181] It is to be emphasized that, despite such references in the literature,[208, 209] the Streptococcus is not causally related to rheumatoid arthritis.

Hogan, Kimura and Thygeson[83] have indicated that rheumatoid arthritis may affect the eye in two distinct fashions:

In the first type the disease may vary in intensity from a mild anterior uveitis to an acute fulminating disease which starts out unilaterally to be followed within months, at most a year, by involvement of the second eye. Duration of each attack is 4 to 6 weeks and the severity of the ocular involvement is unrelated to the degree of joint involvement. Keratic precipitates may vary from the fine, thin lymphoid variety to the heavy, lardaceous, mutton-fat type, or may be absent. Occasionally a fine vitreous haze and a papillitis with edema secondary to the anterior segment disease will appear.

Following repeated attacks, irreversible changes leading to visual impairment occur, although blindness is uncommon. Recovery from early attacks is usually good. Visual loss is due only to the anterior segment changes.

The second variety described by Hogan *et al.* is a chronic smoldering disease commonly associated with the severer forms of peripheral arthritis. Clinically, it appears as a low-grade, torpid anterior uveitis with little congestion, inexorably leading to visual loss through synechiae formation, scarring, secondary glaucoma and complicated cataract formation. These eyes tolerate surgery poorly and the incidence of blindness is high.

According to Short *et al.*,[179] the median time for ocular involvement is four years, although it can precede the joint manifestations and has been reported to appear as late as 12 years after the onset of peripheral joint manifestations.

Juvenile Rheumatoid Arthritis (Still's Disease)

Juvenile rheumatoid arthritis (Still's disease) is a more fulminating disease than the adult variety usually associated with marked systemic manifestations. Fever and hepatosplenomegaly are common. The incidence of uveitis in these

patients has been placed at 8 to 20 per cent.[14, 46] Not infrequently the uveitis antedates the systemic appearance of the disease.

Ocular involvement is invariably bilateral, and despite abundant objective signs, the subjective manifestations may be mild or even absent and the inflammation often goes unnoticed by the child until discovered on a routine examination or because of severe visual loss. The typical ocular triad of band-shaped keratopathy, intractable anterior uveitis, and complicated cataract is considered pathognomonic of Still's disease.[46, 180] The iridocyclitis consists of marked circumcorneal injection, intense flare and cells, and a small pupil which will not dilate because of many fine, closely spaced adhesions of the iris to the lens. In the more chronic stages the injection practically disappears. Posterior segment involvement is secondary to the anterior segment inflammation. The ocular complications are usually unrelated to the severity of the systemic manifestations of rheumatoid arthritis in these children.

Ankylosing Spondylitis (Marie-Strumpell's Disease)

Until recently ankylosing spondylitis (Marie-Strumpell's disease) was regarded as a variant of rheumatoid arthritis. The two diseases are now considered as two distinct entities. Ophthalmologists, however, had long recognized the difference between the two types of arthritis. Whereas only 5 per cent of patients with rheumatoid arthritis have uveitis, some 15 to 30 per cent[11, 14, 25, 108, 124] of patients with ankylosing spondylitis have anterior uveitis.

Perkins[142] points out that three-quarters of the patients with this disease are males in the 20- to 40-year age group, that half of them have elevated erythrocyte sedimentation rates and that the diagnosis of ankylosing spondylitis is made frequently after the uveitis has become manifest, a point which has also been made by Laitinen *et al.*[108] Catterall[25] has found a high incidence of chronic genital infections in these patients, although he has been unable to isolate any specific organism.

In most instances the uveitis is a mild to a fairly severe nongranulomatous type affecting the anterior segment exclusively. Usually the disease affects one eye at a time although bilaterality does occur. Low grade but persistent flare and cells are characteristic. Eventually, useful vision may be lost as in the chronic form of rheumatoid arthritis, through damage created by recurring attacks.

Gonococcal Arthritis

Gonococcal arthritis and uveitis, as noted above, are rarely seen now. The diagnosis of gonococcal uveitis is in itself a difficult one to establish with certainty since all too frequently the urethral discharge has subsided, and the gonococcal complement-fixation test, of questionable value, is not easily available. Diagnosis is made on the basis of an acute plastic exudative uveitis associated with a past history of gonorrhea, or proved smear, and the clinical course of an acute migratory polyarthritis appearing independently or in conjunction with the uveitis. Antibiotics are ineffective at this stage of the disease.

Reiter's Disease

Very similar to gonococcal and to ankylosing spondylitis uveitis—and frequently very difficult to differentiate from them—is Reiter's disease, which has a similar history of urethral discharge, migratory polyarthritis, and recurrent bouts of uveitis. Sacroiliac disease is not uncommon in these patients,[130] and can be separated from Reiter's syndrome only by careful radiological studies of the sacroiliac region. Catteral[25] found an incidence of 23 per cent in 105 patients with anterior uveitis and emphasized the possible role of chronic genital infection in these patients, although no specific causative organism could be found.

Gouty Uveitis

Gouty uveitis, frequently mentioned in the older literature, is not believed to be a true complication of gout but rather a coincidental complication. Dr. A. B. Gutman[71] states that in over 200 patients with gout he has never encountered one with uveitis.

Sarcoidosis

In recent years the relationship of tuberculosis to sarcoid has been defined more clearly with the demonstration that there are basic clinical, epidemiologic and pathologic differences between the two diseases.[178] For example, in sarcoid symmetrical enlargement of the hilar nodes occurs but not in tuberculosis; in sarcoid the pattern of organ involvement is the uveal tract, salivary and lacrimal glands and cardiac and skeletal musculature, whereas in tuberculosis, involvement of these structures is uncommon, pleural involvement being the rule; sarcoid is noncontagious, occurs in rural areas and shows no response to chemotherapy, whereas the opposite is true of tuberculosis. The Nickerson-Kviem test is specific for sarcoidosis, with 85 per cent of sarcoid patients giving positive responses. Lastly, the much discussed anergy to tuberculin has been shown to exist only when the tuberculin is suspended in saline. If a paraffin medium is used instead, the incidence of positive tuberculin reactions in sarcoid patients approaches that of the general population. Furthermore, the dermal insensitivity exhibited by sarcoid patients extends to all cutaneous antigens of the delayed bacterial type.

Should, eventually, the work of Cummings *et al.*[45] be confirmed it would do much to explain the similarities and the differences that exist between the two diseases. These authors, examining a group of 1800 patients with sarcoid, found that all of them came from rural areas located in the pine belt region. In addition to possessing phospholipids and waxes similar to those in the tubercle bacillus, pine pollen was found to have diaminopimelic and mycolic acids, both constituents of the tubercle bacillus, which have also been found in sarcoid lesions. Furthermore, they noted that subcutaneous injections of pine pollen led to the formation of "noncaseating" epithelioid reactions in rabbits.

Interesting as these etiologic considerations are, they do not diminish the importance of ocular sarcoidosis which occurs in 25 per cent [42, 94, 129] of patients with systemic sarcoid. Subacute and chronic anterior uveitis accounts for 55

to 60 per cent of all ocular involvement.[94] When associated with parotid enlargement (4.5 per cent) it is known as Heerfordt's syndrome and when associated with lacrimal gland enlargement (4 per cent) the eponym is Mikulicz's syndrome.[178]

The subacute anterior form of uveitis is less common, usually appearing in the third decade, although we have seen it in a Negro lad only 9 years old. It is ushered in suddenly with pain, mistiness of vision, ciliary congestion, a heavy flare, slowed convexion current and the presence of many fine cells in the anterior chamber. Under local or systemic therapy the attack may subside leaving no sequelae, or, it may merge into the chronic form of granulomatous sarcoid uveitis which often persists indefinitely.

Chronic granulomatous uveitis is usually bilateral, insidious in onset (only rarely associated with an acute crisis), and characterized by the absence of ciliary congestion, the presence of a low grade constant flare with large cells and cellular particles in the anterior chamber and huge "mutton fat" keratic precipitates on the cornea. Nodules of varied size are scattered over the iris surface, usually appearing as discrete masses deep in the iris structure. It is our experience that these become vascularized only rarely and usually when hyalinized. Unless they become hyalinized they disappear rapidly under steroid therapy. There is a high incidence of posterior synechiae formation which leads to secondary cataractous changes. Eventually corneal changes occur as well. A not uncommon complication is intractable secondary glaucoma due to plugging of the exit channels with cellular debris and large protein molecules.

One complication which we have frequently observed is a periphlebitis of the retinal veins.[36] We believe that this is a common finding if the retina is carefully examined. The veins are engorged, and possess a segmented appearance. Frequently they are extremely tortuous, so much so that they resemble the picture found in congenital tortuosity of the veins. Cuffing and sheathing are common. Superficial and deep hemorrhages are often observed along the course of the veins, and occasionally there are noted small exudations adjacent to the veins.

James,[94] in a review of ocular sarcoidosis, stresses the differences between the subacute and chronic forms of uveitis, emphasizing that in the former only transient erythema nodosum and intrathoracic changes occur, whereas in the latter the skin lesions are indolent, the intrathoracic changes permanent, and bone lesions are present. He believes that the more favorable therapeutic prognosis found in those with subacute iridocyclitis may be related to spontaneous remissions independent of therapy with corticosteroids.

Spirochetosis

A. Syphilis

Once incriminated as a cause of uveitis in 30 to 60 per cent of uveitis,[47] the discovery of the Wassermann test has removed syphilis from the speculative realm. It is not believed to be a common cause of uveitis now although the congenital variety is still encountered on occasion.

B. Leptospirosis

Although 16 strains of Leptospira have been reported,[1] the best known clinical example is Weil's disease caused by the *Leptospira ictohemorrhagica.* The occurrence of uveitis as a complication of systemic leptospirosis has been variously reported at from 10 to 44 per cent.[1] The uveitis may appear as early as the second week of illness or be delayed as long as 18 months, but most commonly occurs between the fourth and sixth month of the disease. The uveitis usually consists of a mild inflammation of the anterior segment with occasional vitreous clouding. The disease has a great relapsing tendency and can assume a low grade chronic form although this is rare. Posterior segment involvement is uncommon and is usually regarded as a secondary complication of the anterior segment disease. Leptospirosis and leptospiral uveitis have been rather extensively reported upon in the European and Australian literature where the incidence appears to be considerably higher than in this country.[187] Further information on the types of leptospirosis, serologic data, modes of transmission and clinical manifestations are amply covered elsewhere.[61, 187]

Virus Diseases

The following viral diseases are believed to be commonly associated with uveitis: herpes simplex, herpes zoster, influenza, varicella and lymphogranuloma venereum. More rarely uveitis is found in association with mumps, vaccina, infectious hepatitis and infectious mononucleosis. It has been reported to occur in rubeola, in rubella and in epidemic keratoconjunctivitis.[9, 27, 189]

When a uveitis becomes manifest during the course of a systemic viral disease, such as influenza or one of the exanthemata, or is associated with herpes zoster or simplex, a diagnosis of viral uveitis is easily made. The characteristics of viral uveitis have been described[9, 189] and consist essentially of: a unilateral uveitis (occasionally bilateral) affecting exclusively the anterior segment, with an acute inflammatory response, complicated at times by a hyphema—thought to be characteristic by some[9]—and with little tendency to form posterior synechiae. The course is benign and brief, usually not lasting more than 2 to 4 weeks and leaving no permanent sequelae.

Herpetic viral uveitis should be suspected when uveitis appears in conjunction with the skin or labial lesions of herpes simplex or zoster. Thygeson *et al.*[189] believe that herpes simplex can present as a primary uveitis. Secondary uveitis following herpes simplex or herpes zoster can result in a severe keratouveitis, associated with excessive pain and complicated by secondary glaucoma, and characterized by a stormy clinical course lasting for months that is quite unresponsive to therapy. Hyphema is a frequent complication of herpes simplex uveitis according to Cavara,[9] but Thygeson *et al.*[189] do not feel that it is pathognomonic, although 11 of their 92 patients exhibited it. While the uveitis frequently parallels the keratitis, severe uveitis following the subsidence of the corneal complication has been noted. Occasionally relapses of the uveitis, unassociated with keratitis, have occurred, indicating possibly that the virus becomes fixed

in the uveal tissue and acts in a recidive manner, as noted by other investigators.[151]

The uveitis associated with herpes zoster is usually milder and of much longer duration than that associated with herpes simplex. The association of epidemic keratoconjunctivitis with uveitis has been reported.[9]

To sum up, viral uveitis is rarely encountered as a primary disease of the eye and is usually associated with a systemic viral disease. When in association with one of the exanthemata, or with influenza, the diagnosis is self-evident and the course is usually benign. However, uveitis associated with herpes zoster or simplex can be protracted and associated with such complications as secondary glaucoma and keratitis.

Behçet's Disease

Behçet's disease is a chronic infectious, recurring disease, probably caused by a virus, and characterized by uveitis with hypopyon and aphthous ulcers of the mouth and genitalia. Despite its frequent cognomen of "triple symptom complex" it may involve every organ of the body. Its essential character is recurrence, which may be as short as 1 week or as long as 3 years but averages approximately 2 months. The time interval between and during attacks is gradually prolonged and in 15 to 20 years the disease has burned itself out.

Ocular involvement usually follows the mucous membrane manifestations, although it may appear first or second. It begins unilaterally but within 3 months to 4 years is invariably bilateral. The ocular attacks occur every three to four weeks, consisting of an iritis with hypopyon in more than one third of the cases. Associated with the acute uveitis, marked clouding of the vitreous occurs. The hypopyon subsides within three to four days and the iritis shortly thereafter. The vitreous may remain cloudy for two to three weeks. Following each attack, some decrease in visual acuity occurs and eventually the eye becomes blind. It is estimated that 33 per cent[120] of patients become blind in one or both eyes. Blindness is usually due to: (1) disorganization of the anterior segment of the eye due to: synechiae, formation of a cyclitic membrane, complicated cataracts and pthisis bulba; (2) secondary glaucoma; and (3) optic atrophy.[175a,b,c]

Sezer[175a,b,c] believes that the uveitis is secondary to changes occurring in the optic nerve and in the retina and that optic atrophy is the commonest cause of blindness. Mavioglu,[120] however, found this incidence to be 15.5 per cent, but stated that opacities of the media precluding good visualization of the posterior segment could account for this low figure. The retina is involved early by a perivasculitis with hemorrhages and the occurrence of thromboembolic phenomena in the retinal veins.

A more detailed description of this disease entity is contained in the extentive review of the literature by Mavioglu.[120]

Cytomegalic Inclusion Disease Uveitis

Two reports in the ophthalmic literature[22, 32] have focussed attention upon cytomegalic inclusion disease as a cause of acute uveitis in children, especially

newborns. Cytomegalic inclusion disease, or salivary gland disease, has been emphasized recently because newer virus cultivation techniques have clarified its etiology and facilitated its diagnosis.

The typical syndrome involves newborn or young infants who present with fever, thrombocytopenia and anemia, pneumonitis, gastroenteritis, hepatosplenomegaly associated with jaundice, and cerebral calcifications. Clinically, the picture is very similar to that found in toxoplasmosis.[51]

In Burns' report,[22] which includes considerable background material on the disease, the virus was recovered from the urine and aqueous humor, thus giving direct proof of the virus' ability to involve the eyes. It was his impression that the disease may be a more common cause of uveitis than previously suspected, since in proved cases histologic demonstration of inclusion bodies was not possible after the disease had run its acute course. In other words, the large inclusion bodies can only be identified if they are sought during the acute phase of the disease.

According to Burns, the choreoretinitis in cytomegalic inclusion disease consists of multiple peripheral lesions exhibiting relatively little tissue destruction. This finding was originally noted by Christiansen and his coworkers.[32]

Inasmuch as this disease bears a close clinical resemblance to toxoplasmosis, it is suggested that in those instances where the toxoplasmosis dye test is negative in a patient presenting with cerebral calcifications, hepatosplenomegaly and anemia, examination of the urinary sediment for inclusion-bearing cells be undertaken. Isolation and cultivation of the virus from aqueous aspirations would be more convincing etiologic proof.[51]

5. Toxoplasmosis

Several reviews of ocular toxoplasmosis have appeared recently[8, 24, 65, 81, 82] and much of the material on toxoplasmosis in this article is derived from them.

Toxoplasmosis may appear as a congenital or an acquired infection, both of which may exhibit ocular manifestations. The congenital variety is passed on to the fetus through the placental circulation without the mother giving evidence of any illness during her pregnancy. Maternal immunity apparently prevents subsequent fetal involvement since no mother is known to have given birth to more than one toxoplasmic child. The newborn child usually exhibits all or some of the characteristics of the disease: cerebral calcification, hydrocephalus, retarded mental development, splenomegaly or hepatomegaly, and bilateral chorioretinitis. The ocular lesion consists of a focal retinochoroiditis usually involving the macular area but sometimes affecting the more peripheral retina. These lesions are characterized by regular and dense accumulations of pigment surrounding a central zone of atrophy through which the white sclera may be seen. Often associated with the chorioretinitis there is nystagmus, strabismus, and in some instances microphthalmus. In most instances the parasite localizes in the cells of the retina, not the choroid. There is no organismal invasion of the choroid, which becomes involved by an extension of the inflammatory reaction from the infected retina. The organisms are present in the retina in the self-

elaborated pseudocyst form and, as such, can liberate little antigen for antibody stimulation.

The adult acquired form of toxoplasmosis manifests itself in four clinical types: (1) an exanthematous variety, (2) a central nervous system variety, (3) an afebrile lymphadenitic form, and (4) an ophthalmic form. This classification is based on the work of Siim.[177]

Estimates of the incidence of adult acquired toxoplasmosis are of questionable value since one is never certain that: (1) the uveitis is truly toxoplasmic in nature, and (2) many instances of adult toxoplasmic uveitis may actually represent reactivation of a congenitally acquired disease. (The difficulties associated with making a diagnosis of toxoplasmosis will be discussed later in the section devoted to diagnostic procedures.) Hogan[81] believes that toxoplasmosis accounts possibly for some 15 per cent of all uveitis. Perkins[144, 146] raises this figure to 25 per cent and Woods, Jacobs *et al.*[212] feel that 55 per cent would be more realistic. Cassady[24] increases the figure to 70 per cent.

Frenkel and Jacobs[65] have subdivided ocular toxoplasmosis into two varieties: a proliferative and a cyst type. According to them the proliferative form involves a much smaller percentage of patients and manifests itself as a progressive, smoldering, torpid condition due to the active multiplication of the organisms in the retina. This is the type of disease which persists for many years with exacerbations and remissions leading to eventual excision of the eye for absolute glaucoma. Cyst forms may also be present in this type of disease, their rupture sparking a new proliferative phase. It is believed that the organisms involved are probably of rather low virulence.

In the cyst form of the disease, which probably accounts for the greater proportion of retinochoroiditis, Frenkel and Jacobs[65] postulate that through some change in the patient's humoral status a cyst ruptures and this leads to a marked allergic inflammatory reaction, with vitreous clouding and visual impairment. Animal experiments have indicated that the organisms liberated by cyst rupture are destroyed in the ensuing inflammatory reaction so that the attack and the lesion are self limited. However, multiple attacks may occur.

Identification of any "typical" clinical picture of toxoplasmic uveitis is difficult. Other than an instance reported by Pillat and Thalhammer,[149] it would appear in almost all instances that this is a disease limited to the posterior segment. Any anterior segment manifestations result from an overflow of the posterior segment disease. The lesion may be markedly inflammatory with a complete vitreous haze precluding visualization of a focal area of retinochoroiditis. On the other hand, there may be a small yellow-white inflammatory lesion located on the border of an old, healed retinochoroiditis—the typical satellite lesion. Localization of the toxoplasmic lesion is nonspecific and it may appear anywhere in the fundus, although a central lesion appears to be common in the congenital variety. Perkins,[144] analyzing 77 patients with posterior lesions and positive dye test titers, described them as occurring as macular lesions, as focal lesions along the course of the vessels, as peripapillary lesions, and as focal peripheral lesions. It was not his impression that disseminated choroiditis or periphlebitis and vascu-

litis were toxoplasmic in nature. Reports[159, 206, 212] linking toxoplasmosis to retinal periphlebitis have been discounted.[65, 80a]

While retinochoroiditis following adult infection with toxoplasmosis is not common, it has been reported on several occasions[101, 198] following infection of the lymphadenitic variety of systemic toxoplasmosis.

In brief, there does not appear to be any classical clinical picture which can be associated with toxoplasmosis, other than to say that it evokes a focal lesion in the posterior segment frequently displaying "satellism." These lesions assume potential clinical characteristics of toxoplasmosis only when the dye titer is positive.

Tuberculosis

The once dominant role ascribed to tuberculosis in the etiology of uveitis has undergone considerable de-emphasis in recent years. In 1941, figures from the Wilmer Institute[72] indicated that it was responsible for 79 per cent of all instances of uveitis. In 1954 this figure had dropped to 23 per cent.[212] Current assessment of its importance varies from 0 to 75 per cent[2, 4, 21, 31, 44] with the Central European literature reporting the higher incidence.

The incidence of ocular tuberculosis is not proportional to the incidence of the systemic disease. Ocular involvement rarely occurs during the course of systemic tuberculosis unless there is miliary dissemination. A study by Fritz *et al.*[67] of 2000 Alaskan children, all of whom were affected with pulmonary or extrapulmonary tuberculosis, failed to uncover a single instance of uveitis, tuberculous or otherwise. Kimura *et al.*[105] reporting on the etiology of uveitis in 47 children under 16, found no instances of a tuberculous etiology.

Amsler[4] believes that tuberculous uveitis can be diagnosed with relative accuracy in instances of miliary choroidal tubercles, tuberculomas of the choroid or ciliary body, and in exudative iridocyclitis. In instances of retinal periphlebitis and disseminated choroiditis, the diagnosis is made with difficulty, and rarely in the more chronic forms of uveitis.

The lesion in uveal tuberculosis depends upon the balance between hypersensitivity and immunity in the host. In a young, highly susceptible and hypersensitive adult, the course of the disease can be acute and fulminating with rapid loss of the eye. This type is well illustrated by a recent report from Dvorak-Theobald.[52]

However, the sequence of events in a young adult who was primarily infected in childhood and has, through the years, developed considerable immunity is much less devastating. After a sharp initial inflammatory reaction this type is rapidly walled off. In the choroid, such reactivation is indicated by satellite areas of choroiditis appearing along the borders of old healed lesions.

However, the similarity of any tuberculous lesion of the posterior segment to other inflammatory causes, such as toxoplasmosis, makes differential diagnosis difficult. The presence of a tuberculoma, or a rapidly spreading necrotizing lesion, or the dissemination of miliary tubercles, leaves no doubt as to the tuberculous etiology but in other instances the issue is not as clear-cut.

The ability of tuberculosis to cause a purely hypersensitive type of reaction involving the anterior segment has been described under hypersensitivity in the section on pathogenesis.

The manifold clinical characteristics of uveal tuberculosis due to bacterial invasion and the modifications brought about by hypersensitivity have been well described by Woods.[208]

Tropical Diseases

Helminthis

The incidence of helminthic ocular infestation in this country is small, although in the rapidly shrinking world of the jet age and large population migrations, an increased incidence of these infections can be expected. While uveitis due to nematodes, cestodes and Diptera larvae has been reported, it is the microfilaria of onchocerciasis (a nematode) that is most frequently reported because of its dramatic presence in the vitreous or the anterior chamber. For the reader interested in parasitic infestations in the uveal tract, several reviews are available.[18, 23, 103, 161]

Amebiasis has recently been incriminated as a cause of central serous choroidosis in six patients with proved amoebiasis, and three with suspected amebiasis.[16] This report emanated not from the subequatorial region, but from the flat plains of Iowa.

Leprosy

Leprous iritis is a frequent complication of the ocular involvement in leprosy which occurs in 50 to 90 per cent of all lepers. The reaction may be acute or subacute, has a great tendency to relapse and results in marked iris and ciliary body atrophy which may lead to phthisis bulbi. The iritis may be mild or fulminating and is usually associated with small white globular bodies which represent leproma nodules. Bacilli are recovered from the ocular tissues with ease. The incidence of blindness due to uveal involvement is high. Several recent reviews of ocular leprosy have appeared.[30, 87]

Psychosomatic Factors

The possible role of psychosomatic factors in the causation of uveitis has received little attention in the ophthalmic literature until recently. Schlaegel[167, 168a] points out that patients with uveitis are tense and anxious and he feels that they are predisposed to uveitis. However, he was unable to pinpoint anything specific, although he did feel that in some patients the genesis of the disease was psychosomatic.

Pearlman[142] subscribes to the concept that physical and emotional stress indirectly precipitate or aggravate uveitis. Perkins[145] originally was intrigued by this concept but found that no concrete evidence to substantiate it could be adduced. He did feel, however, that not infrequently attacks of anterior uveitis were precipitated by domestic stress or emotional crisis. No specific pattern of psychologic behavior on the part of the patient fitted in with any form of uveitis.

Diagnostic Procedures in Uveitis

A thorny question that arises in the management of uveitis is the extent of the diagnostic work-up. All too often the clinician, confounded by the absence of a demonstrable cause of the uveitis, resorts to an expensive, time-consuming and usually unrewarding series of laboratory procedures, specialty consultations and radiologic examinations. To a large measure this approach dates back to the concept of foci of infection, which, in the light of present day knowledge, no longer seems tenable. Employing a fixed routine and identical diagnostic procedures in all types of uveitis is never warranted. This comment, of course, excepts instances in which these procedures are being undertaken as part of a research project for the accumulation of statistical data.

The diagnostic approach should be dictated by the results of the ocular examination and an adequate history. In a certain number of instances the diagnosis will be self evident and further investigation unnecessary. For example, uveitis associated with virus diseases, rheumatic diseases, sarcoid, toxoplasmosis or heterochromic cyclitis of Fuchs require no additional facts to establish the diagnosis.

Viruses

Herpetic uveitis (zoster or simplex) should be suspected in the presence of the typical vesicular lesions on the body, especially on the face. Intractable, prolonged uveitis with a past history of an active vesicular lesion should direct attention to this disease.

A self-limited, unilateral uveitis occurring during convalescence from influenza or following an exanthematous disease should suggest viral etiology. Recurrent uveitis with hypopyon associated with mucocutaneous lesions suggests Behçet's disease.

Rheumatic Diseases

The role of rheumatic diseases in the etiology of anterior uveitis is determined by the history, clinical characteristics and laboratory aids.

Rheumatoid Arthritis

No specific etiologic agent has been discovered, although autoantibody formation has been suggested in the absence of any definite proof of infection. However, in this disease the only evidence to date of a circulating antibody is the presence of the "rheumatoid factor" (RF).

The rheumatoid factor is a substance in the serum of adults with rheumatoid arthritis which has the ability to agglutinate sensitized particulate bodies which are used to test for its presence. This factor is believed to be a protein complex of high molecular weight which may have some attributes of antibody.[106] It falls into the class of γ-globulins, with properties resembling heterophile antibody and cold agglutinins. It has been suggested that in precipitating out it may clog up small vessels and account for some of the secondary manifestations of arthritis.[106]

Its presence can be simply determined by the latex fixation test (LFT), or by

the bentonite flocculation test.[12] Both procedures are positive in 85 per cent of patients with rheumatoid arthritis. The sheep cell erythrocyte agglutination test and its inhibition technique modification[217] is considerably more sensitive in establishing the presence of the rheumatoid factor and should be resorted to when the simpler tests are negative and rheumatoid arthritis is still suspected. McEwen *et al.*[121] found it to be especially helpful in instances of juvenile rheumatoid arthritis. In children with anterior uveitis these serologic tests can be of inestimable value in relating the uveitis to Still's disease, especially in the as yet subclinical forms.

In ankylosing spondylitis this test is negative. Here the diagnosis must rest upon the clinical history, usual physical findings, and the radiologist. In most instances this diagnosis can only be made on the basis of radiologic examination of the spine and sacroiliac changes, as subjective symptoms and clinical findings are absent in about 50 per cent of the patients with this disease.[108]

Verhoeff's test for ankylosing spondylitis is considered to be positive when the patient cannot bend his thoracic and lumbar vertebrae so as to bring his chin and forehead into their respective positions on the slit-lamp for examination of the flare and cells in his red eyes.

The gonococcal complement fixation test is not readily available and in any case it is of dubious value. For the diagnosis of gonococcal uveitis one must rely upon history and clinical manifestations of gonococcal infection. The same applies to Reiter's disease.

Sarcoid

An early diagnosis of uveitis due to sarcoid is essential if irreversible damage is to be prevented. Sarcoid uveitis is to be suspected in a patient presenting with a low grade granulomatous uveitis, early formation of anterior and posterior synechae, and the presence of nodules on the iris. According to James,[94] an associated keratoconjunctivitis sicca or conjunctival follicles or both are common in sarcoid and should orient one to this disease.

These findings, coupled with the systemic manifestations, frequently make the diagnosis a simple one.

Helpful laboratory tests are: a reversal of the A/G ratio, a low phosphorus, high calcium, radiographs which reveal osteolytic lesions in the small bones, or enlarged hilar nodes or both are pathognomonic. A positive Nickerson-Kviem test is positive proof in 85 per cent of instances. Biopsy may be necessary in some cases to establish the diagnosis of sarcoid.

Spirochetosis

Syphilis

The usual serologic tests for syphilis will confirm the suspected presence of this cause of uveitis.

Leptospirosis

Not infrequently, leptospirosis is diagnosed by isolation of the causative organism in the blood or urine. More commonly, the demonstration of specific

lysins or agglutinins in the serum is sufficient. The isolation of Leptospira in the aqueous is an uncommon, but most dramatic, etiologic proof.

Toxoplasmosis

Inasmuch as the clinical picture of uveal toxoplasmosis is nonspecific, a presumptive diagnosis can only be made by emphasizing serologic methods.

Sabin Feldman Dye Test

Of all the serologic tests available this is the most reliable. Despite reports[6, 123] questioning its specificity, confirmation from several sources[102, 194] indicate that the test is specific for toxoplasmosis and that cross reactions do not occur.

The diagnostic usefulness of the dye titer in uveitis is considerably impaired by a high incidence of positive dye titers in the population at large. Surveys of a random population reveal that in age group 0 to 10, 5 per cent show positive reactions; in age group 30 to 40, 50 per cent are positive; and in persons over 40 years of age this figure is 65 per cent.[80] As a result, positive dye tests in patients with uveitis must be evaluated with extreme caution. However, the incidence of positive dye titers in patients with posterior uveitis is almost double that of the general population, and also double that found in patients with anterior uveitis.[78, 80, 147, 146] Therefore, the presence of positive dye titers in patients with posterior uveitis should lead one to a consideration of toxoplasmosis in the differential diagnosis. It is to be emphasized that this test is qualitative rather than quantitative and is merely indicative of past toxoplasmic infection. Despite reports of higher dye titers in posterior uveitis, it is not felt[65] that these are of any greater diagnostic significance than low titers.

At the present state of our knowledge, the significance of fluctuations in dye titers in relation to uveitis activity has not been evaluated. This problem is currently under investigation at the Uveitis Clinic at the New York University-Bellevue Center and the Laboratory of Tropical Diseases of the National Institutes of Health.

Skin Tests

The toxoplasmin skin test is a relatively accurate index of toxoplasmic infection which gives excellent qualitative information. Various studies[24, 92, 162] indicate that the skin test is positive in 80 per cent of patients with positive dye titers. It is our opinion that when positive, the skin test yields as much information as the dye test. It is only when the skin test is negative and toxoplasmosis is suspected that the dye test is indicated, since 20 per cent of patients with negative skin tests exhibit positive dye tests. Since the skin test is readily available (Eli Lilly and Company), and the dye test is not, we advise skin testing first as a screening device.

Hemagglutination Test

The difficulty in obtaining the dye test may be solved by substituting for it the hemagglutination test recently described by Jacobs and Lunde.[91, 118] With

sheep red blood cells and a water soluble lysate of toxoplasmic cells, these investigators have prepared an antigen suitable for routine laboratory use. The test is unassociated with the hazards of manipulating live organisms, is simple and inexpensive to perform, and is presumably as accurate as the dye titer.

Agar Diffusion

O'Connor has employed the agar diffusion technique of Ouchterlony as modified by Halbert[131, 132] for demonstrating precipitating antibodies to toxoplasma in the aqueous of patients with uveitis. The finding of precipitating antibodies in the aqueous, but not in the sera, of several patients with uveitis implies ocular antibody production independent of systemic production. These techniques, however, are so delicate that, at this time, they are of great research value but possess little clinical application.

Complement Fixation Test

Complement fixation antibody usually disappears from the serum within a month of contracting the disease, and therefore is of little value in making a diagnosis of toxoplasmosis. The chance finding of a positive complement fixation test, however, would be good evidence of the recent toxoplasmic infection. For clinical use, though, it is of little value.

In summary, any posterior uveitis with a positive toxoplasmin or dye test can be regarded potentially as a toxoplasmic infection. Although no sharp, clear cut clinical picture of toxoplasmosis exists, one should be suspicious of satellite lesions appearing at the site of old, healed lesions—especially those thought to be congenital in nature. Any torpid, long-standing posterior uveitis with gradual focal extension is a possible indication of the proliferative type of toxoplasmosis described by Frankel and Jacobs.[65]

Although toxoplasmosis is currently regarded as the most common cause of posterior uveitis, it is most important to remember that there have been many previous etiologic vogues in the past which were embraced just as heartily as the current one for toxoplasmosis. The patient with an unresponsive, chronic uveitis has, in the past 20 years, been enthusiastically treated for tuberculosis, brucellosis and toxoplasmosis. Likely as not, the uveitis has been unaffected by all forms of therapy; therefore we would like to urge caution in making the diagnosis of uveal toxoplasmosis.

Tuberculosis

The clinical diagnosis of uveal tuberculosis, except where choroidal miliary seeding occurs, is difficult because of the pleomorphism of the lesion and its clinical similarity to toxoplasmosis. This difficulty is further accentuated when the patient exhibits positive tuberculin and toxoplasmin skin reaction. Satellism, hypersensitivity, and organismal invasion of the uveal tract occur in both diseases, giving rise to a similar clinical appearance.

Clinically, tuberculosis should be suspected in a young adult with iris nodules (rule out sarcoid); in a rapid, progressive, caseating lesion, especially in Negroes:

in a severe spreading choroiditis; in the presence of an associated episcleritis, or phylctenular keratoconjunctivitis; in the presence of retinal periphlebitis; on finding satellite lesions; in the presence of a chronic granulomatous iritis.

Convincing proof of uveal tuberculosis, either the purely allergic variety, or that due to actual organismal invasion, is the lighting up of the disease following skin testing with tuberculoprotein[31, 126, 127, 195, 196]—a so-called focal reaction. Such reactions unequivocally indicate that the uveitis is tuberculous in origin.

With the advent of antituberculosis chemotherapy, a new diagnostic tool is available—the therapeutic test (*vide infra*). A sharp response to antituberculosis therapy administered during the course of a severe uveitis would be presumptive proof of a tuberculous origin. Schlaegel[168] has found this test to be so specific that he employs it routinely on all patients with a positive Mantoux and posterior uveitis before administering steroids or other therapy. Unquestionably, this test is of help in diagnosing and treating uveal tuberculosis, but one must always realize that the improvement can be coincidental to spontaneous recovery in many instances. In our own unpublished observations there are a large number of patients who improved rapidly and dramatically without therapy.

The Mantoux test in ocular tuberculosis is of little help when positive since it merely indicates past exposure—usually systemic. It has been shown[76] that patients with uveitis do not exhibit a higher incidence of positive reactions to tuberculoprotein than does a random control population. The Mantoux test is of diagnostic value only when it causes a focal reaction or when it is negative. A negative tuberculin test would almost certainly eliminate tuberculosis.

The Middlebrook Dubos test and its modifications[125, 156] has adherents[54, 59, 165] who believe it aids in making a diagnosis of uveal tuberculosis, while others report that this procedure is of little help.[43, 117]

Helminth

Other than recovery of microfilaria from the aqueous, positive diagnosis of parasitic uveitis is established on the basis of history of exposure, clinical findings, and the pathologic identification of the organism. There are several detailed reviews of this etiologic type.[18, 23, 161]

Fungus Infections

Usually, the clinical picture presents as either a severe purulent endophthalmitis or as a chronic granulomatous inflammatory response. In the latter instance the uveal tract exhibits many small areas of abscesses which are manifested clinically as discrete yellow-white areas which may become confluent with neighboring ones. Invariably these localized abscesses will break down and discharge purulent matter from which the causative organism can be recovered.

Woods[203] feels that the *Histoplasma capsulatum* is one of the most important of the fungi producing uveitis and that it is an important cause of endogenous uveitis in general. Unfortunately, the organism has not yet been recovered from enucleated eyes. According to Woods, the clinical picture is that of a discrete

and more nodular choroiditis, similar to that attributed to chronic brucellosis. He bases the diagnosis on the clinical picture, the presence of old, calcified pulmonary lesions, anergy to tuberculin and a positive histoplasmin skin test.

Therapy

Therapy of uveitis consists of nonspecific measures aimed at allaying the inflammatory reaction, and in specific therapy directed at the cause of the disease.

Nonspecific measures are both local and systemic. The former, consisting of mydriatics and local steroids, are described elsewhere.[128, 208] Systemic measures include the use of parenteral steroids and fever therapy.

Steroid Therapy

Despite the widespread use of adrenocortical steroids in practically all forms of uveitis and the frequently dramatic results achieved, these beneficial effects result only from their potent, nonspecific anti-inflammatory action.

However, associated with this anti-inflammatory effect, a simultaneous inhibition of the defense mechanisms of the body occurs. Thus phagocytosis is reduced or eliminated, fibrosis is curbed, and neovascularization is inhibited.[113, 115, 207, 210] Initially these deleterious effects are not immediately apparent since the well being of the patient as a result of the hormones masks the underlying process. Woods and Wood[214] and Baum and Drobeck,[7] have shown that while on steroids the nonimmune tuberculin hypersensitive rabbit initially does well, but when therapy with the hormones is halted, an almost immediate rebound phenomenon occurs resulting in a soft, caseating, widespread, necrotizing tuberculous lesion.

Clinically, this effect has been noted frequently in the treatment of posterior granulomatous lesions with steroids where new satellite lesions appear adjacent to older lesions which seemed to be improving. The ensuing secondary inflammatory reaction is frequently worse than the primary disease.

Indications for the Use of Steroids in Uveitis

Local and systemic administration of steroids is clearly indicated in the anterior nongranulomatous forms of uveitis. Here, the inflammatory reaction responsible for the reaction is due only to the antigen-antibody reaction and no bacterial invasion or physical irritant is involved. By suppressing the inflammatory reaction the ocular structures are protected until the response of the tissues has returned to normal.

Although it is safe to administer systemic steroids to patients with anterior uveitis, the opposite obtains in most patients with granulomatous, posterior uveitis due to organismal invasion.

The principal indications for systemic steroid therapy in infectious granulomatous uveitis are: (1) involvement of the macula area, and (2) a high degree of hypersensitivity. It is best, when the specific etiology is known, to combine the administration of steroids with appropriate chemotherapeutic agents. In the

absence of an infectious component in posterior granulomatous uveitis, it is permissible to administer steroids without antibiotics.

Methods of Administration

A wide variety of corticosteroids are available for local and systemic administration. These are cortisone, hydrocortisone, prednisolone, methyl prednisolone, triamcinolone, and dexamethasone. All are marketed under various trade names and all are available for local and systemic use. All have approximately equivalent anti-inflammatory effects and similar side effects. The initial dose is usually 40 mg. of prednisolone (or its equivalent) administered daily in divided doses. As clinical improvement becomes manifest the dosage is reduced by 5 mg. daily until a relapse occurs. The maintenance dose is then readjusted to the lowest effective level.

Corticotrophin is used intravenously or intramuscularly. The usual intravenous dose is 40 units administered in an 8-hour drip. The intramuscular dose can be started at 80 to 120 units daily and gradually decreased, depending upon the degree of clinical response evident at each dosage level. As soon as possible, corticosteroids are substituted.

Corticosteroids are preferred because of their ease of administration and the fact that they are often effective locally. However, in certain instances, where rapid and high hormonal levels are desired, corticotrophin is indicated. In severe inflammations which threaten the functional integrity of the eye they are to be preferred.

Subconjunctival administration of steroids is of value in posterior uveitis when systemic administration is contraindicated. In this manner effective concentration can be obtained, whereas locally applied drops have no effect on posterior segment disease. Gordon[69, 70] advises injection beneath Tenon's capsule high under the upper lid. He states that the presence of white crystals under the conjunctiva does not mean that active steroid is present. Currently, we are investigating the clinical value of a repository form of methyl prednisolone for subconjunctival use. The steroid is released gradually over a prolonged period of time, lessening the need for frequent injections and assuring a high level locally in the eye. Preliminary results have been gratifying in a wide variety of conditions. With this technique it is hoped that it will be possible to maintain high ocular concentrations without resorting to systemic administration.

Contraindications to the Use of Steroids

Certain contraindications to the use of steroids should be borne in mind. They are the following:

1. Uveitis

In those instances where the uveitis is suspected of being due to intraocular infection with the following organisms: toxoplasmosis, tuberculosis, fungi, and some viruses. When doubt exists appropriate specific chemotherapy should be administered simultaneously.

2. Infection

In the presence of corneal infections due to fungi, herpes simplex and certain bacteria like the pseudomonas.

3. Increased Tension

Reports have appeared relating ocular hypertension to steroid administration.[109, 115] However, this is relatively infrequent, since in most instances steroids usually help normalize tension, according to Offret and Haye, who reported lowering of tension in 66 per cent of their patients whose uveitis was complicated by glaucoma.[134]

4. Systemic Diseases

In tuberculosis, peptic ulcer, severe hypertension, cardiac disease, mental depression, diabetes, and acute infectious processes unresponsive to antibiotics, systemically administered steroids are contraindicated.

Fever Therapy

The wide use of steroids in the therapy of uveitis has tended to supplant fever therapy in the treatment of this disease. However, some steroid-fast cases may improve following fever therapy. No doubt many of the beneficial results obtained with nonspecific protein therapy are engendered by the stress reaction produced by the pyrogenic reaction as shown by Donn.[48] Nonetheless it would seem that other factors as well contribute to the salutory effects of fever therapeusis. Its effectiveness is perhaps enhanced by capillary dilation, increased permeability of the cells, and a greater blood flow to the diseased tissues, permitting the penetration into these structures of a greater concentration of antibodies and beneficial humoral factors.

It is now realized that the actual pyretic substance in fever therapy is the endotoxin present in the injected material.[116] Further amplification of the role of endotoxin in uveitis can be found in the section devoted to streptococcal uveitis.

Another indication for fever therapy is granulomatous uveitis of doubtful etiology where possible aggravation of the disease by the use of steroids contraindicates these agents. Here, foreign protein is useful and generally safe. Nielson and Kirby[128] queried 30 English-speaking ophthalmologists on their opinion of the use of fever therapy in the treatment of uveitis. Of the respondents 23 indicated that they used corticosteroids in preference to fever therapy, 4 indicated that they preferred fever therapy, and the others employed both modalities with no specific preference.

Other nonspecific anti-inflammatory agents used in the treatment of uveitis are salicylates, 4 to 8 gm. daily, and phenylbutazone, 800 mg. daily. Both drugs are employed rarely now because of the more predictable and superior effects obtained with the adrenocortical hormones. Further details can be found elsewhere.[128, 208]

Several reports[170a, 170b] have appeared stating that chloroquine administration

results in a potentiation of the effect of steroids, permitting lower doses without loss of anti-inflammatory effect. We have had no experience with this combination, but it has been reported that prolonged chloroquine administration may result in the formation of corneal opacities, though reversible upon withdrawal of the drug.[43]

Therapy of Specific Forms of Uveitis

In instances where a specific diagnosis of the associated disease has been made and the etiologic agent is unknown, one is dependent upon nonspecific therapy for controlling the uveitis. The following are examples of this category.

Rheumatoid Arthritis and Juvenile Rheumatoid Arthritis

Since no specific etiologic agent has been uncovered in this disease, one is dependent upon nonspecific measures in treating the complicating uveitis. Therapy of the arthritis with salicylates and butazolidin will frequently produce a beneficial effect upon the uveitis as well. In the milder forms, local steroids and attention to maintaining mydriasis will be sufficient. However, if the inflammation fails to respond, immediate use of systemic corticosteroids is indicated.

If band-shaped keratopathy is present, considerable visual amelioration can be obtained by chelation with sodium versenate.

If cataracts form, they should be removed only as a last resort when visual impairment is extreme, since these eyes do not tolerate surgery very well. Pre- and postoperative systemic corticosteroids are indicated, despite the occurrence of inhibition of fibrosis and delayed wound-healing. Extra corneoscleral sutures should be used.

Ankylosing Spondylitis and Reiter's Disease

These are treated in the same manner as rheumatoid arthritis. Therapy is nonspecific and aimed at blocking the inflammatory reaction with adrenocorticosteroids.

Viral Diseases

With the exception of lymphogranuloma venereum, a rare cause of uveitis, antibiotics are of no avail.

Most viral uveitis, with the exception of herpes simplex, are best and most easily controlled with local mydriatics and steroids. In uveitis due to herpes simplex it is best to withhold steroid therapy because of their deleterious effect on the corneal disease. Here fever therapy would probably be more desirable. The uveitis associated with herpes simplex may be persistent and prolonged, even after disappearance of the corneal lesion. Pain will be considerable and analgesics necessary. Secondary glaucoma is commonly controlled with the carbonic anhydrase inhibitors.

In uveitis due to herpes zoster, Scheie and McLellan[166] have reported dramatic results with corticotrophin administered in a slow intravenous drip with 40 units per infusion.

Sarcoid

Ocular, as well as systemic, sarcoidosis responds to systemic corticosteroids. This disease, which has a great tendency to the rapid formation of anterior and posterior synechiae resulting in secondary glaucoma, must be treated assiduously. There should be no hesitation to use systemic steroids generously, rather than relying on local administration alone. Recurrences are common and it is frequently necessary to maintain hormonal therapy despite the appearance of moon-facies and other secondary changes characteristic of overdosage.

Phacoanaphalactic Uveitis

Immediate treatment of phacoanaphalactic uveitis consists in the use of steroid therapy both locally and systemically—including, if necessary, corticotrophin. If feasible, intracapsular cataract extraction should be performed. Desensitization with lens antigen has not proved very successful.

Behçet's Disease

Despite reports that corticosteroids are contraindicated in the therapy of Behçet's disease[175a, 175b, 175c] we, as well as others,[120] have been impressed with the dramatic and extremely rapid termination of individual attacks following systemic steroid administration.

In addition to steroid administration it has been our experience that intramuscular administration of γ-globulin, 5 to 10 cc. weekly, is of help in controlling the acute attacks and preventing exacerbations.

Vogt-Koyanagi-Harada Disease

Steroids offer the only effective palliative therapy for this disease.[17, 40, 183]

Leptospirosis

Systemic treatment with chloramphenocol and streptomycin is indicated. Local ocular complications are best controlled by local and, if necessary, systemic steroids. Cataract extraction of 2° cataracts is well tolerated in these patients.

Leprosy

This disease is best treated with the sulfones and chloramphenocol. Local manifestations may be controlled with mydriatics and local steroids.

Heterochromic Cyclitis of Fuchs

Local mydriatics are the sole treatment indicated in this entity, since steroids appear to have no effect on the evolution of this disease. Complicated cataracts which appear present no problem since their removal is well tolerated and the postoperative course is uneventful.

Tuberculosis

The direct attack on the tubercle bacillus consists in the administration of isoniazid in divided doses to equal 300 mg. daily for a total of three weeks,

followed by another three weeks with divided dosage totaling 150 mg. a day. Simultaneously, *p*-amino salicylic acid is given in doses of 3 gm. four times a day. Streptomycin is no longer regarded as necessary in the nonfulminating forms and should be held in reserve for acute exacerbations. Therapy is maintained for six weeks. If no improvement occurs one can assume that tuberculosis is not the causative agent. If improvement appears, therapy should be maintained for at least three months. In some instances where there is reasonable certainty that the disease is caused by tuberculosis but fails to respond to the above routine, it may be assumed that hypersensitivity rather than infection dominates the picture. The treatment of choice here is steroid therapy, systemically administered, with simultaneous use of antituberculosis therapy.

Desensitization with tuberculin, while theoretically of value, does not seem to be clinically effective. It is not without danger and treatment must be maintained for long periods of time. It is no longer used routinely in the treatment of tuberculosis of the eye in this country or in England.[81]

Sympathetic Ophthalmia

Systemic steroid therapy has considerably improved the once bleak prognosis in this disease, as is attested by numerous reports.[41, 141, 122] Ideally, sympathetic ophthalmia is best treated initially with daily administration of 20 to 40 units of corticotrophin in an intravenous drip over an 8-hour period. Once improvement had been obtained, corticosteroids are substituted. Forty to sixty milligrams of prednisolone or its equivalent is administered daily and the dosage is gradually reduced until symptoms reappear. At this point the dosage is increased again until control is achieved. Local mydriatics and steroids should be continued throughout therapy. It may be necessary to maintain systemic steroids, gradually decreasing or increasing the dosages according to the clinical picture, for many months, or even years, until the disease burns itself out.

It is our feeling that prophylactic steroids should not be employed routinely following perforating injuries of the eye, especially during the first two weeks. An opportunity to observe the natural unmasked reaction to injury, and to assess its likelihood of uneventful healing with useful vision, is afforded by this 14-day grace period, during which time decision to enucleate may usually be safely postponed. Treatment with steroids may mask unsatisfactory progress of healing, which would make the prophylactic removal of the unsafe eye mandatory. McLean[122] has felt, on theoretical grounds, that steroids should not be used following perforating injuries.

Fungus Infections

Effective chemotherapy of mycotic infections is, unfortunately, not yet available. The two antifungal agents in common use are Amphotericin B and Nystatin, both of which are somewhat toxic when administered parenterally. Administration should be undertaken with the aid of a consultant versed in the use of these agents. Dosage schedule is not fixed and must be determined in each specific instance. It is important to emphasize again the danger of steroid

treatment of mycotic infections since this considerably enhances the infection.

Brucellosis

The antibiotic of choice in the treatment of brucellosis is achromycin and Chloromycetin. Initially this combination should be administered every four hours in 500 mg. doses. After 4 days dosage should be reduced to 500 mg. four times a day. This schedule should be maintained 3 to 4 weeks. It is no longer felt that adjuvant therapy with sulfadiazine or streptomycin is indicated. The ocular manifestations should be treated with local steroids and mydriatics.

Toxoplasmosis

Since Eyles and Coleman[56] demonstrated that pyrimethamine (Daraprim) in combination with sulfadiazine worked synergistically to curb the proliferation of *Toxoplasma gondii* in mice, many reports have appeared of its effectiveness in treating human toxoplasmosis.

Ryan *et al.*[163] were the first to use it in the treatment of toxoplasmic chorioretinitis, reporting clinical improvement in 25 of 29 patients. Many reports on the clinical effectiveness of this therapeusis in the treatment of active toxoplasmosis have since appeared in the literature.[65, 146, 144] The report of Perkins *et al.*[147] deserves further comment. With the use of a double blind test, these investigators rather convincingly demonstrated the beneficial effects of pyrimethamine (Daraprim) in the treatment of circumscribed areas of chorioretinitis in patients with positive dye tests, and the lack of improvement in patients with negative toxoplasma dye tests, or with anterior uveitis.

However, considerable differences seem to exist concerning the effective dosage of Daraprim—varying from 25 mg. daily to 25 mg. per 60 kilos per day. The experiences of some investigators[82, 85, 163] with Daraprim in the treatment of uveitis have been disappointing. Choi[29] has found, in rabbits, that in order to secure effective concentrations of Daraprim, toxic serum levels are required.

Kaufman *et al.*[96, 96a, 97] have recently clarified therapy considerably in studies on the pharmacologic action of Daraprim in man and the nature of virulence of the *Toxoplasma gondii*. They demonstrated that the serum levels of pyrimethamine were entirely dependent upon its absorption from the gastrointestinal tract, which varied from person to person. Elimination, however, is constant but slow, so that serum levels would, over a period of time, become more significant due to pyrimethamine accumulation in the blood. They found that administering a high "loading dose" resulted in the rapid establishment of high serum levels of pyrimethamine maintained thereafter by a small daily maintenance dose. These investigators noted that a serum concentration of 0.3 mg. per 100 ml. of pyrimethamine resulted in few toxic reactions. Thereafter, toxic manifestations were directly proportional to serum levels. The authors suggest that the "loading dose" of pyrimethamine should be 100 mg. given twice on the first day to be followed thereafter with 25 mg. twice a day, combined with 1 gm. of triple sulfas four times a day.

Kaufman and co-workers[96a, 96] further found that the virulence of the different strains of toxoplasma varies considerably and is directly proportional to the invasiveness and the rate of multiplication of the organism. They found, for example, that the slow-growing 113-CE strain was not nearly as lethal to mice as the more rapidly dividing RH strain of *Toxoplasma gondii*. They also felt that the effectiveness of pyrimethamine was much greater in animals infected with the rapidly dividing RH strain. Furthermore, concentrations of pyrimethamine which killed a rapidly growing RH strain, allowed the 113-CE organism to survive in many instances. The authors point out that metabolic antagonists which are used clinically to kill cancer cells and bacteria are always more effective when the cells or organisms are dividing rapidly. By analogy, they point out that pyrimethamine, which is used as a metabolic antagonist competing for the folic acid pathway, is perhaps ineffective clinically because the infection is due to one of the less virulent, slowly dividing strains of toxoplasma such as the 113-CE strain.

Other explanations for the failure to respond to antitoxoplasmic therapy are enumerated:

1. The uveitis under treatment may be mistakenly attributed to toxoplasmosis.
2. The focus of necrosis may be so great that it prevents penetration of the drug.
3. The serum levels of pyrimethamine may be too low.

At the New York University-Bellevue Uveitis Clinic we employ the following routine in adults with toxoplasmosis: Pyrimethamine (Daraprim) 25 mg. four times a day for 3 days; then 25 mg. three times a day for 2 days to be followed by 25 mg. twice a day thereafter; sulfadiazine, 1 gm., four times a day for 5 days and then thereafter 0.5 gm. four times a day. If a markedly allergic component is present, such as follows cyst rupture, or if the lesion appears to be encroaching upon the macula, prednisolone, 40 mg., daily (or its equivalent) is administered for 2 days with gradual tapering to 20 mg. daily. This regimen is maintained for 3 weeks. If at the end of this period no improvement has occurred, the pyrimethamine and triple sulfas are discontinued. However, in those instances where it seems, because of the clinical picture, that the organism is one of low virulence, the amount of pyrimethamine may be increased for a short period of time while observing the patient for signs of drug intoxication. The dosages are adjusted for children according to their age.

Complete blood counts and urinalysis are performed weekly; twice-weekly where signs of intoxication appear. If thrombocytopenia becomes manifest, 3 mg. of citrovorum factor (Leucovorin, Lederle) is given intramuscularly daily. Frequently, this will be adequate to control the thrombocytopenia—if not, pyrimethamine must be stopped. We do not administer the citrovorum factor routinely since we feel it may compete for the pyrimethamine. Patients are urged to drink copiously because of the sulfa therapy.

Recently Fair[57] has proposed that immunity to toxoplasmosis can be achieved by stimulating antibody formation through repeated injections of skin antigen.

Jacobs and Melton[93] have shown, however, that live vaccines are far superior to the killed vaccines in producing immunity in guinea pigs providing mild strains of *Toxoplasma gondii* were used. It is conceivable that this approach can be used in humans to increase their resistance to toxoplasmosis once the the disease has been acquired. However, here as in any form of desensitization therapy, the danger of focal reactions must be considered. For the present this technique's value seems to be mainly experimental.

Research Trends

A survey of the ophthalmic literature of the past decade reveals an ever increasing emphasis on experimental investigation. This has been especially true in the field of uveitis where the introduction of many new concepts and techniques—primarily from the field of immunology—have considerably broadened our understanding of this disease.

Excellent reviews of hypersensitivity mechanisms and their applications to the study of uveitis are to be found in the transcripts of the Uveitis Symposium held at Princeton in May 1959[190] and in a review article by Sery.[174]

It is now believed that certain diseases, such as thyroiditis, endophthalmitis phacoanaphylactica and, possibly, sympathetic ophthalmia, are caused by sensitization of the host to his own tissues and that in the future other diseases will be explained on the basis of similar autoallergies. There is some suggestive evidence that other types of uveitis may arise on a similar basis.

The experimental production of autoantibodies has been made possible through the use of Freund's adjuvant: heat-killed tubercle bacilli suspended in mineral oil. When mixed with any antigen, Freund's adjuvant has the effect of vastly potentiating the antigenic response. For example, by injecting Freund's adjuvant plus tissue extracts such as thyroid, testis, epidermis, and central and peripheral nervous system myelin into experimental animals, it has been possible to produce autosensitization to similar tissues in the host. It is interesting that the original organ extract need not be autogenous to provoke autoallergy. Antibodies to the host's tissue are produced. The reaction is not elicited if the adjuvant or the tissue which is being sensitized is omitted.

These observations may offer a new approach to the study of uveitis. Recently, Bullington and Waksman[19] discovered that in producing experimental allergic encephalitis (EAE), in which the body forms antibodies to its own central nervous system myelin, three-quarters of the animals simultaneously developed an anterior nongranulomatous uveitis. However, when they employed Freund's adjuvant and uveal tissue, they produced a mild form of experimental allergic encephalitis but were unable to provoke any uveal reaction. This last finding is at variance with the previously mentioned (under sympathetic ophthalmia) work of Collins.[38, 39]

Besides this challenging introduction of a new concept in the pathogenesis of uveitis, these experiments also have the immensely practical aspect of providing a working model for the experimental production of uveitis unassociated with trauma or manipulation of the globe.

Further investigations suggesting the possible role of autoantibodies in the production of uveitis were performed by Fernando,[58] who found that bovine albumen, tagged with radioactive iodine, when injected into the vitreous of nonsensitized rabbits, accumulated most intensely in the ciliary body, lens and anterior hyaloid, structures where the P.A.S. stain in the same sections was most intense (the P.A.S. stain is specific for mucopolysaccharides). This predilection of antigen for tissue polysaccharide suggested the formation of a polysaccharide-antigen complex resulting in autosensitization. All of his animals developed anterior uveitis with cyclical exacerbations and remissions. Thus clinically, allergic uveitis developed on the basis of the original sensitizing injection only; no second or "shocking" dose of antigen was necessary.

The abundant vasculature of the uvea appears to be a factor in the local production of antibodies *in situ*. Experiments performed by Witmer[200, 201, 202] indicate that such local production of antibodies occurs in the reticuloendothelial cells of the uveal tract. Simultaneous estimations of serum and aqueous antibody levels were performed. Results indicated that in the first week following infection the antibody level was low in the serum but nevertheless higher than in the aqueous. However, by the tenth day, coincident with the appearance of plasma cells in the choroid, the antibody content of the aqueous rises so rapidly that its concentration becomes three times that of the serum. This would indicate that local antibody formation can and does occur in the uveal tract and that it is most likely a function of the plasma cells of the reticuloendothelial system.

O'Connor, employing the agar diffusion technique of Ouchterlony,[131, 132] demonstrated the presence of precipitating antibodies to toxoplasma in the aqueous, but not in the sera, of seven patients and postulated that this indicated local ocular antibody production. This technique has made possible a qualitative determination of aqueous antibodies. With further refinements it may be possible to test for the presence of multiple antibodies simultaneously with minimal amounts of aqueous.

Another technique with an enormous potential for the study of antigen-antibody reactions occurring in the uveal tract is the fluorescent tagged antibody technique of Coons. Witmer,[201] tagging leptospiral antigen with fluorescin, was able graphically to demonstrate its uptake by the uveal tract in eyes previously sensitized to this antigen. Roberts[160] used this same technique to demonstrate a common reaction by the basement membranes of the eye to the same antigen which provoked a uveitis.

Diagnostic aqueous aspirations in the course of uveitis have had a much greater vogue in Europe than in this country. In recent years this technique, previously performed principally to determine the presence of cellular elements and microorganisms, has been modified to allow serologic study of the aqueous. Laffers and Bozsoky[107] and Remky[155] claim that estimation of the serum ASLO permits a definite diagnosis of streptogenic uveitis. Remky also feels that it is of help in making a diagnosis of tuberculous uveitis.[156] Witmer,[199] while allowing that serologic examination of the aqueous can be of help, does not feel that this is too often the case.

Ogielska,[136] examining the cellular sediment of aqueous aspirations, has devised a "dynamic cytogram" which gives an index of the protective mechanisms of the eye. This index is determined by dividing the sum of the monocytes and reticuloendothelial cells by the sum of the lymphocytes and leukocytes. Three successive aspirations are required and if ascending values for the index are found, the prognosis is good. An unchanging, or a descending index indicates a poor prognosis. The successful identification and quantitative analysis of these formed elements in the aqueous is no mean feat in view of their varied origins and rapid destruction.

Kapuscinski and Ogielski and co-workers[98a, 99, 137] have used the Kolobolocki color reaction—a solution of dye with silver salts forms a permanent color when united with toxins which cannot be decolorized with potassium permanganate—to determine the hypersensitive *versus* bacterial type of uveitis in rabbits. According to them this test was of value in humans in determining whether the uveitis was bacterial or hypergic in nature—the reaction being positive in the former instance.

It would be perhaps advantageous for investigators in this country to re-evaluate the bacterial, cellular and humoral aspects of the aqueous. Other than the excellent investigation by von Sallmann[192] and virus isolation studies undertaken at the Proctor Foundation,[189] the American literature is particularly sparse on this subject. In view of the more recent methodologic approaches that are available, it would seem well worth while repeating and amplifying these studies on the aqueous.

In summary, it seems that the opportunities for the elucidation of the pathogenesis of uveitis appear brighter today than ever before. This optimism stems from the great strides which have been made in the basic sciences, the application of this knowledge to the study of uveitis, and the availability of unusual laboratory aids and techniques for implementing these investigations. While the fundamental breakthroughs will probably come from the laboratory it will still be the task of the clinician to evaluate and test these newer concepts in the patient who is, after all, the finest experimental subject.

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Special Article

SAFETY LENS MATERIALS*

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The use of spectacles is so ordinary that, like automobiles without seat belts, their very commonplace appearance and thousands of numbers about us, belie their deadly potential. Spectacles should be protective shields to the eyes rather than sources of injury in themselves. Distant foreign objects hold no monopoly on trauma; spectacle fragments themselves can be more devastating than rocks or chips. Tom Dickinson,[1] of Sarasota, Florida, has recently collected 36 cases of ocular injury from broken spectacle glass; 10 of these resulted in industrial blindness. Four were from lead weights used while fishing. Three resulted from fist blows; 14 were from flying objects such as nails (3), rocks (5), baseballs (3); 2 were from simple falls, and 3 from automobile wrecks—injuries which might have been prevented by wearing seat belts.

This carnage of eyes could have been prevented by simply preparing spectacle prescriptions in safety materials rather than crown glass. Spurred by compensation insurance problems, industry has done an excellent job in preventive ophthalmology.[2, 3] The National Society for Prevention of Blindness has on record the names and addresses of over 12,000 American workers—members of the "Wise Owl Clubs"—whose eyes have been saved by safety lenses. About 20 per cent of this number are bilateral cases. We must do as well for the do-it-yourself craftsman—and for ourselves.

A study of 1800 nonoccupational eye injuries by the Arkansas Department of Public Welfare[4] points out that 35 per cent of these injuries occur in the first decade of life, 25 per cent in the second, and the remainder are about equally distributed through subsequent decades. Males are significantly more involved than females.

John R. Fair,[5] on the basis of Korean War Injuries (1950–54), has called for 3 mm. thickness, tempered (heat toughened) lens, "Eye Armor," for all troops in combat and in firing training.

EARLY HISTORY

Primitive protective efforts date from the 15th century, but occasional concern in the modern sense of safety did not appear until about 1840. Dirt catching wire mesh, heavy plate glass and quartz, optically poor mica, and soft celluloid

* Presented at Frank E. Bunts Educational Institute, Cleveland, December 9, 1959.

received some attention in the late 19th and early 20th century. The advent of automobile goggles sparked the development of plate glass foundry goggles which, in 1913, cut the eye accidents at American Steel Foundries by 75 per cent Walter G. King, the first safety director of American Optical Company, channeled the resources of this major manufacturer with a large distributing and promotional organization to perform a great service in disseminating safety concepts.

CURRENT MATERIALS

Current safety lens materials are classifiable into: (1) laminated glass, (2) heat toughened glass, and (3) organic plastics.

Laminated Glass

The earliest successful laminations for safety purposes were accomplished in the first years of this century but not until the stimulus of World War I did manufacturers—primarily French and British—produce quantities of triplex or sandwich glass.

At a time when heat treated glass was being developed in the United States, interlayer and edge sealing problems compounded the difficulties facing laminated lense acceptance in this country.

Laminated lenses have never achieved the popularity here that they enjoyed in the British Commonwealth, though discoloration and interlayer breakdown problems have been essentially solved since World War II by the introduction of polyvinyl butyral (Saflex, Monsanto Chemical Company). On drop ball testing and other low velocity blows, these lenses fracture at essentially the same impact as does ordinary crown glass. Small particles may fly from the inner surface as the lens is struck on the outer surface. Experiments with test spheres under 1 mm. in diameter and fired at high velocities of 250 to 1600 feet per second failed to achieve penetration of laminated lenses but frequently these small steel spheres would fracture the front lamina. Bausch and Lomb manufactured these lenses under the name Laminex and American Optical Company manufactured them under the name I-Safe. They are still produced under the name Motex by Optical Industries of Indianapolis.

Heat Toughened Glass

The heat treating or thermal toughening of glass developed in the 1870's hand-in-glove with the method of tempering steel to make armour plate. Technical understanding of empirical processes—as is so often the case—did not come for another 50 years. The modern process of heat treating is applied to lenses after polishing and edging is completed. It is particularly important that polishing be accurate because fracture systems generally start in surface flaws. Polishing adds strength to glass, just as immersion in hydrofluoric acid will, by taking away a defective layer from the surface. Scratched or pitted "safety lenses" should be removed from use because such blemishes reduce impact resistance and the wearer is lulled into false security when wearing such a marred lens.

Automatically timed, table top size heat treating units are suitable equipment for even small optical shops. These units electrically heat the lens to a temperature just below its softening point for 50 to 300 seconds depending on the weight or average thickness. Time must be reduced for colored lenses because of their greater heat absorption. Both surfaces are then rapidly cooled between blasts of cold air creating a fixed state of compression in the chilled surface layer. Glass is inherently strong in compression. The inner core, which cools more slowly, contracts with the formation of radial tension lines, pulling against the surface layer as the spokes in a bicycle wheel pull against the rim. On the basis of this compression tension ratio, the impact resistance is increased from 3- to 7-fold.

These strain lines are easily identified and quantitated by inspecting a heat treated lens between two sheets of Polaroid film with any common light source. Isochromic lines appear in such a lens marking the locus of stress distribution of uniform value. Where the principal axes of stress are parallel to the axes of the Polaroid film, there will be light extinction or isoclinic lines which appear black. These should be balanced and symmetrical in the radii of the lens—as are the spokes of a wheel. The greater the contrast between the isoclinic lines and the background illumination, or the narrower are the isoclinic lines, the greater will be the strain within the lens. Contrast should be medium grade, however, for excessive strain may produce brittleness. Lens with irregular pattern have unsatisfactory distribution of strain and low impact resistance; such lenses must be discarded or retempered with greater precision.

Peripheral isoclinic rings are seen in well toughened lenses, particularly minus lenses where there is greater edge thickness. Such rings indicate even distribution of edge compression and hence edge resistance, but should not "break through" to the geometric edge of the lens.

Though such strain systems may diminish slightly over 15 years or more, they are permanent within practical use of spectacles and are not exhausted by repeated impacts that fail to break the lens.

The ophthalmologist's aide, in checking lenses should quickly inspect them between a folder of Polaroid film for proper isoclinic lines just the same as she checks for centering and power.

Tempered lenses must not be subjected to drill holes and should be mounted in plastic rather than metal frames to increase further their shock resistance.

Heat treated lenses for industrial use must have a minimum thickness of 3 mm. (Federal Specifications for Goggles GGG-G501 b July 13, 1944) and withstand a test impact of a 45 gm. steel ball freely falling for 50 inches. Corrected curve blanks in prescription ranges are available to meet this 3 mm. minimum specification (B & L Industrial Thickness Orthogon; Tillyer A-O Super Armor Plate; Titmus Industrial). Similar properties can be given to thinner lenses for nonindustrial use, using minimum thickness blanks of 1.8 to 2.2 mm. These are lighter in weight, more attractive, more acceptable for street use, but offer slightly less impact resistance. Prescription range blanks are available to the optician in this thickness under the names Tempross Tillyer (American Optical Company), Tuffx 2 mm. (Titmus), 2.1 mm. Orthogon

(Bausch & Lomb), or Dress Safety 2.2 mm. (Shuron). Other trade names, such as Hardrx, Safe-Rex, and Tuffrx are applied to these semiophthalmic thickness lenses, by their jobbers.

Plastic Materials

Since the introduction of optical lenses in the 13th century, no fundamental change has been made in the basic lens materials until 25 years ago when more durable optical plastics of the Plexiglas, Lucite, Perspex type were introduced.

Modern optical plastics are generally classified according to molecular linkage into linear polymers which are thermolabile (thermoplastics), or cross linked polymers with three dimensional structure which are thermosetting. The latter have structural organization somewhat like diamond and inability to be softened by heat after once being hardened by it.

The long, flexible, linear polymers may contain thousands of carbon atoms in the main chain. Methacrylates and polystyrenes are common examples of these plastics having excellent refractive characteristics, but as with cellulose acetate (Kodapak), they are too soft for practical lens use. Less expensive and industrial lenses (Optilite B, Tulca, Dockson No. 11, Watchemoket 44OC, Watchemoket CSC, I-gard, etc.) made from the methacrylates have not proved durable.

A considerably harder, cross linked polyester resin known generically as allyl diglycol carbonate (CR-39, Selectron, Kriston) has been much more widely used in the development of harder resin lenses (Armorlite, Enduron, Optilite A, Plastough, Plastolite, Plasticor, AOlite, Safe-T-vis, Orma 1000 (Lentilles Ophthalmiques Speciales, Paris)).

A basic polymer when processed by different manufacturers will often end up with altered mechanical characteristics, though the reproducibility of optical properties from batch to batch with any one producer's methods is quite good. Accuracy of plus or minus 0.001 should be expected in the refractive index.

EVALUATION AND SPECIAL CHARACTERISTICS

Optical characteristics in heat treated and laminated glass lenses closely parallel the characteristics of conventional crown glass aside from the birefringence in polarized light as seen in tempered glass. Similarly, refractive characteristics of nearly 200 available clear plastics fall in patterns closely related to conventional crown glass.

Physical and chemical factors in these lenses are more critical to their usefulness, and such factors are integral to the very purpose of changing from plain glass to protective materials.

Several thousand tests have been run at the University of Louisville[6] to evaluate safety factors in lens materials of different types, thickness curvature, and even of different processors.

A.

Surface hardness or scratch resistance is a minor problem in the heat treated lenses and a major problem in the plastic lenses. These issues have been clouded

by multiple, empirical tests often without translatable results. Heat treating or thermal toughening of glass, because of increased resistance to elastic deformation, does make it slightly more suspectible to scratching and abrasion which in turn lowers the impact and optical qualities of the lens. Softness becomes insurmountable in polystyrene, cellulose acetate, and methacrylate products where Rockwell E scale indentation values range widely from +30's to −30's. Allyl resin lenses produce more consistent values ranging from mid 40's, and within this range, lenses from each processor group within 2 to 5 points.

B.

Impact resistance to the drop ball (velocity 17 to 20 feet per second) approximates low velocity accidents in civilian life. Measures in terms of minute, high velocity (250 to 1600 feet per second) pellets simulate aeronautical and military circumstances. High velocity studies of Rose and Stewart[7] show that minute, high energy particles burrow through the skin of heat treated glass, at roughly one-third the velocity needed to penetrate the more elastic, conventional crown glasses. As the high velocity particles are increased in diameter above 2 mm. then the heat treated lens shows increasing resistance as seen in the low velocity tests. Comparison of industrial thickness (3.5 mm.) heat treated glass with rabbit corneas, reveals corneal tissue to be more resistant to penetration than the lenses; since the lenses break at velocities less than required to penetrate the cornea, they are, for 1 mm. missiles, not a protection but rather a hazard due to secondary missiles. Against allyl resin lenses, these 1 mm. pellets produce no more than a barely visible dent even when fired at maximum velocity.

Average minimum drop distances required to produce fracture of any type in various heat treated glass and plastic lenses has been quantitated with the seven-eighths inch steel ball. Impact resistance generally decreases with temperature, as the ductility of the lens decreases. Impact resistance also increases with the cube of the lens thickness.

Among the plastic lenses, the allyl resins, particularly exemplified by Armorlite, afford, in our opinion, consistent and high impact resistance. Among the glass products, heat treated, industrial thickness (3 mm.+) lenses offer the greatest, low velocity, impact resistance. As in the case of hardness, a wide scatter of impact resistance values is found in the methacrylate lenses.

The prescription strength also affects the impact resistance, particularly in reference to symmetry of the surface. Thus, increasing spherical and decreasing cylindrical powers produce increasing resistance. Similarly, more plus and less minus refractive power are associated with increasing resistance. In lenses of very low impact resistance, as crown glass, it is difficult to correlate drop distances with refractive power.

C. Fracture Patterns

Quantitation of minimal impacts required for fracture does not tell the entire story of protection, because many of the softer lenses yielding small cracks and linear fractures at low impact will hold together in a suitable frame and prevent eye damage. Crown glass and the inner layer of laminated lenses spall into

malicious spicules. Among plastic lenses, I-gard and the methacrylate lenses yield the most benign fracture pattern, but this is awkwardly related to the lens softness.

D. Thermostability

Allyl resin lenses withstand temperatures through the boiling range, but I-gard, Optilite B, and cellulose acetate products show distortion at 165 to 180°F.

E. Chemical Resistance

Chemical resistance of the optical plastics is generally somewhat less than that of glass; methacrylates are particularly susceptible to acetone and lacquer solvents. Contrariwise, allyl resins are quite resistant to these agents. Common alcohols, household ammonia and carbon tetrachloride are generally without effect on optical plastics.

F. Flammability

All of these plastics are flammable but are difficult to ignite with household matches and generally burn less readily than conventional spectacle frames which are often made of cellulose nitrate. The fire risk with such plastic lenses is much less than with usual frames.

G. Density to Roentgen Rays

Because radio-density depends on atomic weight, organic plastics, composed of oxygen (16), hydrogen (1), carbon (12), and nitrogen (14), offer very little impediment to roentgen rays. X-ray visualization of small fragments is essentially impossible. It is fortunate that the very practical level of impact resistance in plastic lenses generally precludes the need of x-ray localization for fragments.

ADVANTAGES OF PLASTIC LENSES

1. Much greater impact resistance, especially in the cross linked, allyl resin lenses to *both* larger, low velocity and smaller, high velocity missiles.
2. Fragmentation when it does occur usually yields larger and more obtuse segments than when glass lenses are broken.
3. Weight is 50 to 60 per cent that of glass.
4. Radiation filters for sun use or welding are easily made in uniform density regardless of refractive power by applying a surface dye to the allyl resin. Among the better commercially available products are: Armorgrey medium and dark; Armorlite sunmaster green in three shades; Enduron neutral grey, and green 1 and 2; Safe-T-Vis in green 1, 2, and 3.
4. Transmission in the visible spectrum is slightly better than with glass, and transmission in the ultraviolet range of 290 to 320 mμ wave length is very low.
6. Less tendency to thermal fogging particularly in the thinner plastic lenses.
7. Less affected than glass by welder's splatter or thermal shock of hot metals.
8. Manufacture by moulding or casting eliminates surfacing procedures and

makes for ultimate, economical mass production of highly perfect aspheric surfaces.

9. Replacement, usually because of surface abrasions, is not an emergency as with broken glass.

10. Critical polishing and birefringence are not necessary to increase impact resistance as with glass.

DISADVANTAGES OF PLASTIC LENSES

1. Relative softness.

2. Thermoplastics may be distorted by modest blasts of heat as in opening an oven door, but thermosetting plastics void this.

3. Slightly greater susceptibility than glass to chemical attack.

4. Edging if done on an optician's "blue stone" tends to fill the pores of the stone, but instruments such as the American Optical Duomatic bevel edger overcome this difficulty. Glass and plastic lenses should not be edged alternately on the same edger.

5. Resurfacing is impractical and in general runs counter to the plastic lens program of eliminating surfacing procedures.

6. Plastic lenses are flammable though difficult to ignite, and burn more slowly than most spectacle frames.

7. Optical plastics have less heat absorption than glass, but this property increases with thickness.

8. Metal coatings, such as aluminum, copper or Iconel, cannot at present be satisfactorily bonded to plastic.

9. Cost of plastic lenses is slightly more than that of glass in the lower strengths and increases sharply in higher powered prescriptions.

INDICATIONS

1. Heat treated industrial thickness glass (Super-Armorplate, Bal-Safe, Super-tough, Armorglas, Bensafe, Savotex, Hardex, Super-Safety, etc.) is indicated in grimy, hazardous occupations (other than welding and exposure to minute, high velocity missiles), vigorous sports and high minus cylinder correction for children. Thick appearance and heavy weight are relative contraindications.

2. Heat treated semiopthalmic thickness glass (Tempross, Safe-Rex, Hardrx, Tuffrx, etc.) is indicated in higher plus spherical corrections for children or individuals in only relatively hazardous occupations—including hyperopic mothers of young children. They are contraindicated in minus cylinders, high minus spheres, frankly hazardous occupations, for welders, or as plano-protective lenses.

3. Allyl resin lenses in ophthalmic thickness (Armorlite ophthalmic, Enduron, AOlite, Safe-T-Vis, etc.) are indicated for corrections other than high minus cylinders and are especially desirable in high minus spheres.

4. Allyl resin lenses in industrial thickness (Armorlite industrial, Plastough, Optilite A, Plastolite) are indicated in hazardous occupations especially with

exposure to welding or minute particles, violent sports and minus cylinder corrections, except where heavy grime and perspiration require frequent wiping. Where temperature changes give rise to fogging they are especially desirable.

5. Crown glass may be used for individuals confined to sedentary lives or as reading glasses only. They are contraindicated for all children, sportsmen, hazardous occupations, automobiling, or as plano-protective lenses.

6. Methyl methacrylate, cellulose acetate, and polystyrene may occasionally be used as disposable cover lenses but are generally contraindicated as lens materials because of thermolability and softness.

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Clinical Practice

ORBIT

INTRAORBITAL HEMANGIOMA

Review of the Literature and Report of Case

D. V. Hubbell, K. H. Abbott and R. L. Kasper

The Division of Nervous Diseases (Neurosurgery), College of Medical Evangelists, and the Neurosurgical Service, White Memorial Hospital, Los Angeles, California

Bull. Los Angeles Neurol Soc., 1959, *24:* 9

After discussing the classification of orbital tumors in general, the author gives a good review of the subject of orbital hemangioma. The commonest clinical manifestations are proptosis, blurred vision, and diplopia. One case is reported in detail and this was operated on by the transcranial route. The result was satisfactory except for a ptosis and a reduction in vision from 20/30 preoperatively to 20/100 postoperatively.

Comment: As an advocate of the approach to orbital tumors through the lateral wall (Kronlein), I would like to point out that a ptosis seems to be a logical sequela of the transcranial approach. Some damage to the levator muscle seems inescapable if the orbit is explored from above.

A. B. Reese

NEOPLASM

IMMUNOLOGY OF CANCER

M. M. Black and F. D. Speer

The Department of Pathology and Clinical Pathology, New York Medical College, New York, New York

Internat. Abstracts Surg., 1959, *109:* 105

The authors bemoan the fact that so little of the work in cancer immunology has been done on cancer-bearing patients and on spontaneous cancer in experimental animals. Most of the work is concerned with viral or tissue-culture studies, or both, with transplantable tumors, and with antigenic properties of tissues *in vitro*. This is all the more regrettable when it is considered that from the available data pertaining to immunologic phenomena in spontaneous cancer, evidence indicates an association with variable degrees of antigenic changes.

The lymph-node hyperplasia and reactivity as well as the lymphocytic infiltration associated with cancer is consistent with response to antigenic stimulation. However, to date there has been no unequivocal demonstration of circulating serum anticancer antibodies.

The authors feel that there is a need for information regarding *in vivo* reactions of the cancer patient's lymphoreticuloendothelial system against his own cancer cells or antigenic fractions thereof, or both, with particular reference to the stage of the disease. The stage of the disease is important because cancer cases tend to have reactive nodes at the time of surgery and degenerative nodes at the time of autopsy.

Comment: This paper is timely because of the current interest in cancer immunology stimulated by the proof of a previously surmised fact that cancer cells usually invade the peripheral blood stream. These embolic cancer cells disseminated over the body are kept dormant for a very long time or their growth is completely inhibited by some immunologic forces. Cancer cells have been identified in the venous blood draining tumor areas in over 60 per cent of patients (Engle) and in the peripheral blood in 12 per cent of operable cancer and 50 per cent of inoperable cancer (Engle; Roberts).

Therefore, it does not seem to be a question of whether or not cancer cells metastasize but a question of whether or not they can survive and grow at these sites.

The report of Westerveld, Brandon and Zeeman raises the question as to what we are accomplishing by enucleation for malignant melanoma of the uvea. Only 3 out of 23 patients over 60 years of age who had had an enucleation for uveal melanoma reached an age compatible with their life expectancy; 19 died of metastasis and 1 of intercurrent disease at an earlier age. The younger patients fared appreciably better. It suggests the possibility that the primary site might favor immunity.

Present concern over cancer immunology may presage an important break-through in therapy directed towards stimulating resisting forces.

A. B. Reese

RETINA

OCULAR MANIFESTATION OF RENDU-OSLER'S DISEASE

M. RAVAULT AND G. BONAMOUR

J. med. Lyon, 1959, *950:* 693–697

The authors review the general and ocular manifestation of Rendu-Osler's disease (hereditary and familial telangiectasis). Generally, this disease manifests itself as a telangiectasia of the skin and particularly the mucous membranes such as the lip, buccal cavity, under surface of the tongue, gums, nasal and oral mucous membranes, and bronchial, genital and anorectal mucous membranes. The ocular signs are a telangiectasis of the skin of the lids and of the conjunctiva. Also, retinal hemorrhages and degeneration of the elastic fibers in the arterioles of the retina and choroid, as well as Bruch's membrane is seen. A rather typical case is reported and this case, in addition to the general manifestations showed telangiectasis of the palpebral conjunctiva.

The relationship of this disease to Coats' disease is suggested and also they felt that there was some relationship to the syndrome of pseudoxanthoma and angioid streaks of the retina.

Comment: It is interesting to note that in this article a possible relationship is claimed between Rendu-Osler's disease and Coats' disease. This possibility has been mentioned in the past, and evidence supporting this view was given by me in an article entitled "Telangiectasis of the Retina and Coats' Disease." I have never personally seen any connection of this syndrome with that of pseudoxanthoma elasticum and angioid streaks of the retina, nor seen the connection between this disease and the so-called phacomatoses (tuberous sclerosis, von Recklinghausen's disease, and von Hippel-Lindau disease) which has been claimed by some in the past.

A. B. REESE

DIAGNOSIS

APPRAISING THE TUBERCULIN TEST

EDITORIAL

New England J. Med., 1959, *261:* 355

There is no question that when properly conducted the tuberculin test can substitute effectively for a routine x-ray study of the chest. The loss of the more specific information about chest disease is more than offset by the avoidance of unnecessary cost and radiation exposure.

Some caution is needed to be certain that old tuberculin is fresh, and the concentration used in the test material is important. Five units (0.1 ml. of 1:2000 O.T.) will not cause untoward reactions, and yet will still identify almost all patients with active tuberculosis. Higher concentrations may be used if patients are demonstrated to be unreactive to 5 or 10 units. However, if over 100 units is used (over 0.1 ml. of 1:100 O.T.) reactions occur that are not related to infection by either the human or the bovine tubercle bacillus.

In children the patch test is useful, but it is comewhat less specific than the intradermal injection of the Mantoux procedure. True anergy to tuberculin is rare among patients with active tuberculosis and is usually associated with lymphoma or terminal tuberculous infection.

EXTERNAL DISEASE

ELEMENTARY-BODY VIRUS ISOLATED FROM CLINICAL TRACHOMA IN CALIFORNIA

L. HANNA, P. THYGESON AND E. JAWETZ

Francis I. Proctor Foundation, University of California Medical School, San Francisco, California

Science, 1959, *130:* 1339–1340

A 36-year white machinist, a long-time resident of San Jose, developed a red left eye on January 10, 1959, with moderate yellow discharge and a nontender left preauricular lymph node. On February 12, a similar conjunctivitis developed in the right eye, with marked photophobia. On February 16, the inflammation in the left eye suddenly increased markedly, and gross keratitis appeared. Clinical examination on February 17 revealed bilateral papillary hypertrophy, with buried follicles of the upper tarsi, microscopic pannus and corneal infiltrates and palpable preauricular lymph nodes. Scrapings from the upper tarsal conjunctivas showed many inclusions typical of trachoma. Bacterial cultures were negative.

Conjunctival scrapings were collected on February 17 and 19 in broth-saline containing streptomycin (1000 μg./ml.). After 1 hour at 4°C. they were injected into the yolk sac of 6- and 8-day-old embryonated eggs. In this first egg passage there was no mortality, and no elementary bodies were seen in smears of the yolk sac stained in accordance with Macchiavello or Giemsa techniques. Elementary bodies were seen in five of six eggs sacrificed on 9 and 10 days after inoculation. In the third egg passage all embryos died between the 4th and 8th day after inoculation, and elementary bodies were seen in profusion. At present this virus strain (Bour) in the seventh egg passage has an egg LD_{50} of $10^{-4.5}$. The elementary bodies conform in size and in staining properties with those grown by others from trachoma patients. Four monkeys (*Macaca cynomolgus*) were inoculated in one eye with a 20 per cent yolk-sac suspension of sixth passage virus and in the other eye with normal yolk sac. Two to six days later they all developed follicular conjunctivitis, and conjunctival scrapings contained many typical inclusion bodies.

The patients' serum, drawn on February 19, fixed complement in a 1:64 dilution with psittacosis or Lygranum antigens. Antigens prepared from a yolk-sac of virus (Bour) fixed complement with antisera to psittacosis virus (4).

This seems to be the first isolation of an elementary-body virus of the psittacosis-lymphogranular group ("trachoma virus") from a typical case of trachoma arising in the United States. Many intriguing questions are now under study including the relationship of this virus (Bour) to inclusion blennorrhea and to the elementary-body viruses isolated from trachoma in other parts of the world,

the toxin production and pathogenic potential of this agent, and its biological and epidemiologic characteristics.

Comment: This report is of interest as it marks the first isolation of an elementary-body virus of the group chlamydozoaceae from a case of typical trachoma in the United States.

In April 1959 a case of acute conjunctivitis occurred in the left eye of a technician working in the laboratory of Drs. Snyder, Murray and Bell at the Harvard School of Public Health. Typical inclusions were present in scrapings from the upper fornix and an elementary body virus was isolated by them. This case was of interest because of its short duration (less than one week) and because of the presence of hemorrhages under the bulbar conjunctiva. This case will be reported.

Few ophthalmologists practicing in the United States will ever see clinical trachoma, and inclusion blennorrhea of both the infantile and adult types seems to be disappearing. Nevertheless, the isolation of specific agents from these diseases is a milestone in etiology and provides abundant confirmation of the infectious nature of these elementary bodies, originally demonstrated by Thygeson with bacteria-free filtrates over 25 years ago.

Studies are now in progress to determine whether vaccines derived from purified elementary bodies can stimulate active immunity to trachoma in humans.

HENRY F. ALLEN

TRACHOMA AND INCLUSION BLENNHORRHEA

RUSSELL J. BLATTNER

J. Pediat., 1959, *55:* 405–407

(The article embodies a review of recent work on trachoma and inclusion blennhorrhea, drawn from the literature.)

It is noted that laboratory research in trachoma has not been as productive as that in other virus diseases, primarily because a satisfactory study of the viral agent requires the employment of higher primates or human volunteers.

Infection of the eye in both trachoma and inclusion blennhorrhea can be detected by the presence in the conjunctival exudate or scrapings of inclusion-bearing epithelial cells seen in appropriately-stained preparations. The agents are virus-like in some respects, and rickettsiae-like in others. They are susceptible to the sulfonamides and the broad-spectrum antibiotics, and are regarded as of the psittacosis-lymphogranuloma group of obligate intracellular parasites.

Recent work on yolk-sac isolation of the viruses of trachoma and inclusion blennhorrhea is cited as evidence that these viruses do multiply in the yolk sac and can adapt to either the yolk sac or the human host. A study is also cited of the isolation of virus from inclusion blennhorrhea by the demonstration of the presence in several types of tissue of the characteristic inclusion bodies, which resemble those of trachoma.

Reports are noted of two family groups from whom the virus of inclusion blennhorrhea was isolated. Both cases involved conjunctivitis of the infant. One

case was confirmed by yolk-sac inoculation and transfer to the eyes of young baboons, in which the typical inclusion bodies were demonstrated. This strain of inclusion blennhorrhea virus was demonstrated to be very similar to the trachoma virus and to members of the psittacosis-lymphogranuloma group in appearance and in possession of the complement-fixing antigen. It is suggested that infections caused by members of this group be diagnosed early, and their susceptibility to sulfonamides and broad-spectrum antibiotics is restressed.

Comment: It is now well established that trachoma virus can be propagated in series and in quantity in the yolk sac of the developing chick embryo; strains are now available for study from many parts of the world. It is certain also that this virus is a member of the psittacosis-lymphogranuloma group of atypical viruses and that it possesses the common complement-fixing group antigen. As a consequence of the successful cultivation of the virus, much new information on its biological properties has been obtained, particularly as to the nature of a soluble toxin associated with the elementary body. Experiments are now under way to determine whether prophylactic vaccination is feasible.

At the time of writing, the cultivation of the related virus of inclusion conjunctivitis has not yet been confirmed, but confirmation is certainly to be expected. Study of the two viruses in culture should then yield much needed information as to their differences and similarities, and should settle certain disputes which have arisen in connection with various clinical and epidemiologic studies in the past.

PHILLIPS THYGESON

COMPREHENSIVE REPORT ON SECONDARY MYCOSES IN DISEASES OF THE PALPEBRAL MARGIN, THE CONJUNCTIVA AND THE CORNEA

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Ophthalmologica, 1959, *138:* 108–118

Mycological investigation of healthy eyes in patients suffering from some other disease may prove to be useful. It may be that the saprophyte-parasite relationship of the fungi to the host is dependent on the state of the host at the given time. Fungal infections may occur in the eyes as primary invaders or they may be due to fungi which have been residing in the tissues but only become pathogenic when some other local ocular disease or systemic disease influences the eye and thus allows the fungus to become pathogenic.

Among the 20 secondary oculomycoses 12 types of fungi occur as follows:

1. *Aspergillus flavus*, in 4 cases
2. *Penicillium crustaceum*, in 2 cases
3. *Aspergillus sp.*, in 2 cases

4. *Mucor cornealis*, in 2 cases
5. *Acremonium corda*, in 2 cases
6. *Scopulariopsis brevicaulis*, in 2 cases
7. *Aspergillus fumigatus*, in 1 case
8. *Mucor sp.*, in 1 case
9. *Oospora floccosa*, in 1 case
10. *Sterygmatocystis nigra*, in 1 case
11. *Achorion schönleini*, in 1 case
12. *Aspergillus niger*, in 1 case

Of the 12 fungi 8 were types of Aspergillus, 4 of them of the *Aspergillus flavus* group. The primary disease of this series of 20 cases with a clinical aspect of two diseases was caused by a virus in 13 of the cases; 7 cases only were suffering from diseases caused by bacteria.

Since 1934 the author has investigated ophthalmologic-mycologic conditions with his aim defined to include incontestable mycetogenic diseases of the eye as well as the study of the fungi of the healthy eye or of the eye attacked by other diseases. It was found in the course of this research that even the fungi which some authors have treated as saprophytes, are not entirely indifferent. On the one hand the organism is on the defense against the vital functions of these fungi, such as metabolism, fermentation, nutrition, propagation, growth, and so on, on the other hand it reacts in response to them. It was also proved that occasionally they are transformed into parasites and as such may cause pathologic changes. This was another argument in favor of studying the fungus flora of the healthy eye.

Another result of these investigations was the observation that the fungi considered as saprophytes are apt to aggravate the pathologic changes and diseases due to different origin, and also to prolong their course. The author has frequently observed this in the simultaneous occurrence of fission fungi and mold fungi. For example the inflammation of an eyelid infected by one of the fungi mentioned or of a similarly attacked meibomian gland could often hardly or not at all be treated by conventional therapeutic methods; combination with antimycotic treatment, however, showed remarkable results, even though no mycotic clinical picture was present. On the other hand cases were observed where the presence of pathogenic fungi apparently had a therapeutic effect on the existing disease; in this respect *Aspergillus flavus* should be mentioned in the first place.

Of course there is also the possibility of another type of encounter between fungi, bacteria and viruses: a neutral attitude. This was convincingly observed in an ulcus catarrhale caused by Streptococcus and a keratomycosis caused by *Acremonium corda* neither of the two diseases interfered with the other.

Comment: Dr. Fazakas has made an interesting suggestion as well as a very timely one when he recommends that routine cultures and analysis for fungi be done on normal and diseased eyes. It is apparent that the current literature is demonstrating a great desire for many observers to appear in print with observations of fungal infection of ocular structures. It is quite evident that ophthalmologists throughout the country are becoming

aware of and diagnosing intraocular and external ocular infections with these organisms. This may suggest an increasing incidence of this disease due to steroids or antibiotics or both as well as other factors such as increased index of suspicion for the disease. Dr. Fazakas' suggestion, if followed, may very well yield useful information. Many of our corneal ulcerations, chronic lid and conjunctival infections might be of this origin. A single negative fungal culture, scraping, staining, should not be used as positive proof for the nonexistence of a fungal etiology. Repeated searches using different techniques are essential and the cooperation of an interested microbiologist, extremely useful.

IRVING H. LEOPOLD

LENS

ENZYMATIC FACTORS IN EXPERIMENTAL GALACTOSE CATARACT

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Science, 1959, *130:* 1473

Six Rochester colony white rats were put on a cataractogenic galactose diet and six others were fed a control dextrose diet. When the rats on the galactose diet began to show the first signs of ophthalmoscopic evidence of cataract formation (peripheral subcapsular vacuolization), on the 12th to 14th days, the animals of both groups were killed. Their lenses were immediately assayed for glucose-6-P dehydrogenase and 6-P-gluconate dehydrogenase activities by the method of Glock and McLean. The lenses of the galactose rats showed a marked inhibition of glucose-6-P dehydrogenase activity, averaging 13.8 units with a range of 7.9 to 18.8. This was approximately 45 per cent lower than the value obtained for the dextrose group. The 6-P-gluconate dehydrogenase activity was essentially the same for both groups.

This experiment was repeated with 14 rats in each group. Two animals in each group were sacrificed at the 4th day and at varying periods thereafter. The activity of glucose-6-P dehydrogenase showed a significant decline at the 4th day and continued to fall until the 16th day, when it leveled off at approximately 60 per cent of normal. The level of the 6-P-gluconate dehydrogenase showed no change in the lenses of either group of animals. The apparent inhibition of soluble protein synthesis, as measured by the micro-Kjeldal method, did not occur until the 8th day of galactose feeding.

In vitro experiments were performed in which the soluble protein fractions obtained from paired lenses of normal rats were incubated with (1) an excess of

galactose-1-P to glucose-6-P in the media or (2) with glucose-6-P as the sole substrate, or with sucrose added. An average of 20 per cent inhibition of glucose-6-P dehydrogenase occurred, while the 6-P-gluconate dehydrogenase activity remained unimpaired.

The inhibition of glucose-6-P dehydrogenase by galactose-1-P apparently occurs before any observed inhibition of soluble protein synthesis. An inhibition of monophosphate shunt may therefore be implicated in the pathogenesis of experimental galactose cataract.

Comment: This brief article records achievement of the goal of every chemical pathology worker—to find a specific enzyme system affected in a disease process. The demonstration here that the first oxidative step in the hexose monophosphate shunt is inhibited by galactose-1-P and that later production of the enzyme for this step is inhibited, represents just such a finding for experimental galactose cataract. Since galactose-1-P accumulates in congenital galactosemia secondary to the galactose-1-P-uridyl transferase deficit, the mechanism of cataract formation in each disease may well be explained by these findings.

ALBERT M. POTTS

SURGERY

POSTOPERATIVE MODIFICATION OF OCULAR RIGIDITY

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Ophthalmologica, 1959, *138:* 169–174

The rigidity of the sclera has an important bearing on measurement of ocular pressure by the tonometer. In 1955 Friedenwald gave a coefficient of rigidity of 0.0215, and considered figures above or below this erroneous. The present study is designed to determine modifications of ocular rigidity following operations on the sclera. The coefficient of rigidity is determined by Friedenwald's method. Although results are only relative, they are significant since comparison of the different groups are made with the same techniques of measurement.

Aphakic eyes which have been operated upon for cataract have lower coefficients of rigidity than control aphakic eyes, but after a year they become normal.

Eyes treated for glaucoma by iridencleisis resulting in normal pressure and in very greatly reduced pressure were compared with controls. While some doubt has been expressed that the coefficient of rigidity actually is constant at different levels of intraocular pressure, our measurements taken 2 months after operation show that when the eye has regained its normal pressure after operation, it has also regained its normal rigidity. On the other hand, if the decompression has been very great, the rigidity is significantly reduced, sometimes for several years.

Before operation the coefficient of rigidity was 0.0202 in eyes with detached retina; the slightly higher-than-average figure is attributed to the large proportion of myopic eyes in this series. Friedenwald and some others find that myopia reduces scleral rigidity. We have grouped together eyes operated upon by superficial diathermy and by lamellar resection of the sclera, since ocular rigidity does not vary significantly following the two procedures. Over 6 months after operation, the coefficient of rigidity in eyes successfully operated upon was still lower than that in controls. Since we have not followed any of these cases over 18 months, we do not know whether they will eventually become normal. However, the rigidity of two eyes treated by retrocilliary diathermy was normal 4 years after operation, and a larger number of applications are usually made in retrocilliary diathermy than in diathermy for relief of retinal detachment.

In conclusion, surgical operations involving incision or diathermy of the sclera reduce the coefficient of rigidity, and the duration of the change varies with the operation. These observations are important since they must be taken into account in measuring intraocular pressure after operation, or measurement of pressure must be taken using Goldman's tonometry by applanation.

Comment: The decrease in scleral rigidity following various surgical procedures (cataract extraction, filtering operations, detachment surgery, etc.) is variable as to its duration and occurrence from eye to eye. When it occurs it is of importance clinically, for the reduction in scleral rigidity leads to underestimation of intraocular pressure by Schiotz measurements with one weight. This is likely to provide false security to the ophthalmologist following his glaucoma patients. Such false measurements by Schiotz tonometry account for a definite percentage of presumed surgical successes.

BERNARD BECKER

MUSCLES

DIPLOPIA IN THE PERSON OVER 50

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Geriatrics, 1959, *14:* 385–390

Diplopia is most commonly due to sudden loss of coordination between the two eyes. The diagnosis is easily made by having the patient close first one eye and then the other. If the diplopia disappears on closing either eye, then obviously it is caused by using both eyes together and its presence indicates the loss of proper coordination. In rare instances, diplopia may persist when one eye or the other is closed. If this occurs, the condition is monocular and the result of incipient cataracts or other opacities of the media.

Binocular diplopia, with which this discussion is concerned, may be of two types. In the first, the patient perceives two different objects simultaneously occupying the same place; in the second, he perceives the same object occupying two apparently different points in space at the same time. This second type is by far the most common in adults.

It is not surprising that diplopia of sudden onset should cause a sense of confusion in the patient, but interestingly enough he may often not identify this sense of confusion with actually seeing double. He may describe his subjective sensations as blurring, or as a feeling of unsteadiness, or even as vertigo. This failure to recognize double vision as such may be because the images, instead of being separate and distinct, are overlapped, giving an impression of indistinct margins.

Diplopia usually has a relatively sudden onset when it occurs in patients over 50 years of age. In order for a patient to appreciate diplopia, he must previously have had normal binocular vision with approximately equal vision. If an eye with very poor or no vision deviates either in or out, there may be no

diplopia. Diplopia may occur as the result of any displacement of one eye by a local lesion, such as a tumor of the orbit, or by a fracture of the walls of the orbit, direct injury to one or more of the extraocular muscles, or an inflammatory or hemorrhagic lesion. In such instances, the cause of the diplopia is obvious.

Diplopia of sudden onset not associated with any sign of such local involvement suggests a lesion affecting the nerve supply of one or several of the extraocular muscles. Since the involved eye does not coordinate with the sound eye, the lesion is usually unilateral, and unilaterality indicates a nuclear or infranuclear lesion of the third, fourth, or sixth cranial nerve.

Any patient past the age of 50 who suddenly exhibits diplopia should have a careful physical examination with particular emphasis on the cardiovascular system. Regardless of whether this examination reveals positive findings, the patient should also have a complete neurologic examination. Finally, routine blood chemistry examination should be carried out, with particular reference to blood sugar, since diabetes mellitus must be ruled out.

Patients who have suffered trauma to the head present no diagnostic problem. They are usually worse immediately after the injury and gradually improve with time. With good fortune, they may recover completely. If a diagnosis of intracranial neoplasm has been established, the treatment is neurosurgical. The degree of recovery will depend on the extent of the neoplasm and the amount of surgical trauma necessary for its removal. If diplopia persists beyond the immediate postoperative period, it will almost certainly be permanent. When a patient with diplopia has evidence of cardiovascular disease, either hypertensive or arteriosclerotic, and no other cause of the diplopia can be discovered, the cardiovascular disease is assumed to be the causative factor. Treatment is then directed toward the type of disease present. In case of recent, sudden onset, the paralysis will usually clear completely or partially over a period of several days or months. Any residual paralysis persisting after a period of several months is likely to be permanent and should be dealt with as such.

Treatment in each patient, whether the diplopia is due to these or other causes, such as aneurysm, diabetic neuropathy, or various less frequent conditions, should be aimed at the underlying disease. The outcome will depend on the amount of damage to the nerve fibers and may range from return of normal function to loss of all function. Immediate relief can be obtained by patching one eye or the other, and, in certain intractable cases, this may be the only form of treatment that is in any way successful. The choice of the eye to be occluded is largely empirical and should depend entirely on the patient's comfort. A specialist is not needed to carry out this procedure.

There are, however, additional forms of treatment which require the services of an ophthalmologist. The simplest of these is the use of prisms, in the form of clip-ons or incorporated into the patient's correction. The amount of prism and its proper placement depend on a number of specialized tests which can usually be made only by the ophthalmologist.

Surgical treatment may be necessary in a few selected cases, but it should be considered only when the condition shows no change and when there is no

longer any prospect of either spontaneous improvement or improvement as the result of any specific therapy. It is most beneficial in cases of simple lateral rectus paralysis; in this condition, transplantation of slips from other muscles had proved effective in partially restoring abducting action of the globe. In cases of complete and permanent third nerve paralysis, palliative surgery may be attempted, but there is little prospect of success. It may be possible to shift the paralyzed eye so that on casual inspection it appears straight, but true binocular vision is practically never achieved.

Comment: This article seems to be directed mainly at nonophthalmologic physicians. As such it is an excellent summary covering diagnosis, etiology and treatment. However, there are three minor points worthy of discussion. He separates binocular diplopia into two types: seeing two different objects simultaneously in the same place, and seeing the same object in two different places. The first is caused by the stimulation of the fixating fovea and the deviating fovea simultaneously by different objects. The second is caused by the stimulation of the fixating fovea and a peripheral area of the retina of the deviating eye by the same object. The first has been called visual confusion by Swan, and the second is true diplopia. This is more than just a quibble over terminology for later in the paper the author states that in order for a patient to appreciate diplopia, he must previously have had normal binocular vision with approximately equal vision. This is not true, for a patient with 20/200 or 20/400 visual acuity in one eye due to macular degeneration, "hole" or chorioretinal scar may still be incapacitated by diploia if the peripheral retina is functioning. Secondly, he states that surgery is of greatest benefit in cases of simple lateral rectus muscle paralysis, and recommends the transplantation operation. I feel that surgery on the horizontal recti alone should be tried before resorting to the transplantation of slips from the vertical recti. The value of such transplantation procedures alone is not well established, and the simpler recession of the ipsilateral medial rectus and resection of the paretic lateral rectus may restore single vision in the central and nonparetic fields. Whether the transplantation operation can do more than this is problematical. Finally, he states that patients with a superior oblique paralysis rarely have such severe symptoms as to warrant surgery. This again is the opposite of my experience as this muscle has two main actions, depression and intorsion, so that even if the patient can position his eyes to neutralize one element, the other still makes fusion difficult. As this muscle is used in the reading position, it is most bothersome. Tucking of the paretic superior oblique alone or combined with a weakening procedure on its direct antagonist, if contracture is present, may enable the patient to regain comfortable binocular vision in the reading position.

PHILIP KNAPP

Basic Sciences

PHYSIOLOGY

SYMPOSIUM: OCULAR EFFECTS OF IONIZING RADIATION AND RADIOTHERAPY

Tr. Am. Acad. Ophth. & Otol., 1959, July-Aug., 429–500

BASIC CONCEPTS: ORIENTATION

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The purpose of this symposium is to provide a background for the understanding of radiation ophthalmology. A great deal of difficulty was encountered in choosing a title. The first suggestion was amended to the precise but cumbersome title, "*Some* Aspects of *Certain* Radiations of *Possible* Interest to *Some* Ophthalmologists." After much discussion this was abandoned in favor of the more adaptable, though less informative, title the symposium now bears.

The electromagnetic spectrum is a continuum of wave motion varying from infinitely long wave lengths at one end to infinitely short wave lengths at the other end. At the long end are the radio waves, whose wave lengths are ordinarily presented in units of meters, but in the high frequency ranges the waves may be as short as a few centimeters or less. In this latter region they are often called microwaves. Then come the infrared rays, with wave lengths varying from 20,000 mμ to slightly less than 1,000 mμ. Continuous with the infrared rays is the visible portion of the spectrum comprising the octave approximately from 800 to 400 mμ and subdivided into the colors of light. Next comes the ultraviolet portion, which, in turn, is subdivided into the long ultraviolet portion with wave lengths greater than 300 mμ and the short ultraviolet portion with wave lengths less than 300 mμ. This latter contains the highly significant band called abiotic, between 300 and 260 mμ. Shorter than the ultraviolet are the grenz rays, which, as their name implies, are on the border separating ultraviolet and x-rays. Grenz rays have wave lengths of the order of 0.5 to 0.1 mμ.

Next in order of length come the x-rays with wave lengths in the general range of 0.03 to 0.005 mμ, with those on the long end being referred to as "soft" x-rays and those on the short end as "hard" x-rays. The wave lengths of x-rays will actually be determined by the voltage used in their production. Ordinarily

those generated with less than 50 kilovolts are referred to as soft x-rays, while those generated with more than 50 kilovolts, and this may extend up to many million electron volts, are referred to as hard x-rays.

γ-Rays are identical with x-rays except that they are derived from radioactive sources rather than from artificial acceleration of electrons. Their energies are usually measured in terms of electron volts. The differentiation of γ-rays from hard x-rays is, therefore, more a matter of historical semantics than of physical quality.

Cosmic rays, at the extreme short end of the spectrum, are derived from interstellar space and have wave lengths of the order of 10^{-4} mμ or less.

Whether or not these electromagnetic radiations will have an effect on the eye will depend on the manner in which their energies are dissipated in tissue, and thereby on their penetration, as well as on a variety of factors at the cellular level comprehensively designated as radiosensitivity. For the purposes of this symposium, attention will be confined to the so-called ionizing radiations and the manner of absorption or the types of lesions produced by other types of radiation will not be considered.

The ionizing portions of the electromagnetic spectrum are those in the range of grenz rays or shorter. They owe their name and their biologic effect to the fact that their absorption of energy is associated with the ejection of an electron and consequent formation of ion pairs. Whether or not they penetrate into the eye, or through the eye, will depend on their respective energies. Grenz rays and the softer x-rays will be absorbed entirely in the superficial layers of the eye and will produce only a keratoconjunctivitis; while the harder x-rays, those with potentials of 100 or more kilovolts, will penetrate the eye and may cause opacification of the lens and retinal changes in addition to keratoconjunctivitis.

In addition to the ionization produced by the electromagnetic spectrum, probably by wave motions, atomic particles may produce ionization in tissue and may have effects quite similar to, if not identical with, those of the ionizing portion of the electromagnetic spectrum. The atomic particles of most concern at present are the α-particles, made up of charged helium atoms; the β-particles, which are free electrons (and called cathode rays when artificially produced in electron accelerators), and the neutrons. These, too, will have effects on the eye as a function of their penetration and manner of energy dissipation.

The α-particles will not penetrate effectively more than a fraction of a millimeter and, therefore, have no serious consequences (or usefulness) in ophthalmology. The β-particles will penetrate tissue in accordance with their initial acceleration, but those with average energies of 0.34 million electron volts, as in radium D, or 0.80 million electron volts, as in radioactive strontium (Sr^{90}), will not penetrate more than a few millimeters. They will cause keratoconjunctivitis and, with sufficient exposure, cataracts. On the other hand, neutrons bearing no charge will penetrate tissue effectively and have all the biologic effects exhibited by hard x-rays or γ-rays. Thus neutrons may cause not only a superficial keratoconjunctivitis but cataracts and retinal changes as well. In fact, because of the greater ion density they produce, the neutrons are several times as damag-

ing, that is, as cataractogenic, as x-rays and γ-rays, compared on the basis of the amount of equivalent energy loss in tissue.

Biologic Effects of Radiation and a Discussion of Radiologic Units

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To those familiar with the rapid and localized effects of topical medication, the slow but progressive nature of radiation damage is somewhat mysterious. Unlike visible or infrared radiation, with which the immediate and temporary effects may be noted because of the large amount of energy absorbed superficially, the delayed macroscopic appearance of effects of ionizing radiation is due to progression from submicroscopic areas of damage, where the energy has been absorbed, until they spread to include the entire cell. There is also the gradual increase in damage due to the increase in the number of cells that have been killed or injured. The period between the radiation exposure and the appearance of injury is called the latent period. Actually, the basic effects of radiation are instantaneous, but they are so minute as to escape attention until the damage has progressed to larger units, causing histologic or cytologic damage that can be detected.

In general, two types of ionizing radiation must be considered: electromagnetic or wavelike radiation and particulate radiation. In electromagnetic radiation, there is an inverse relationship between frequency and wave length; in other words, the shorter the wave length, the greater the frequency of the oscillations. The quality or the energy of a beam of electromagnetic radiation may be characterized by the energy at which it is generated, the inherent filtration, and the half value layer. The energy of particles may be expressed as $E = 0.5\ mv^2$. Particles vary in mass (m) and in velocity (v). Only the highest energy particles approach the speed of light, whereas all the electromagnetic radiation moves at this speed. The particles used in radiation biology and in radiation therapy are the α-particle; the β-particle; and the proton, a positively charged particle present in the nucleus, with a mass number of 1 and an atomic number of 1. The neutron has a mass equivalent to that of the proton; it is also found within the nucleus, but it has no charge.

The steps in the production of a biologic effect are (1) the production of ionization, (2) the formation of active radicals, and (3) the production of toxic compounds. The degree of response of tissues to irradiation may be affected by such things as the oxygen tension, vascularity, and temperature. Many tissues can be made more resistant by lowering oxygen and respiration during irradiation. Some chemicals have been found to afford some protection if present before and during the radiation exposure. Other substances, such as bone marrow

and spleen extract, given after radiation exposures seem to accelerate the regeneration, and in many cases they seem to replace damaged cells by viable donor tissue

Irradiation of the eye involves cells that vary widely in their degree of mitotic activity, metabolism, and function. The cornea is in an area of rapid exchange of fluid and gases, and is therefore probably in a state of high metabolism. It is apparently highly radiosensitive, because cell division is impaired by relatively low doses and widespread damage may show up very rapidly after exposure. On the other hand, if damage has not been excessive, recovery may soon be practically complete, because the regenerative capacity is high.

The lens, by contrast, is possibly in an area of lower oxygen tension. It probably operates at a lower metabolic rate, and cell proliferation is rather slow. The most noticeable effect of radiation in the lens is the production of abnormal fibers. These abnormal fibers and degenerating cells produce vacuoles and polar plaques. If the exposure is high enough, the degeneration continues and produces complete opacity.

The retina is susceptible to radiation damage and the threshold is not excessively high, but the replacement of cells is rather good. The muscle and connective tissue of the eye are somewhat resistant as very little cell division is involved. The eyelashes and adjacent skin and bone are comparable in their reactions to similar tissues in other parts of the body.

Early Lenticular Lesions Resulting From Ionizing Radiation

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Certain early morphologic sequelae produced by the passage of ionizing radiations through living ocular tissue are discussed in this paper. The biologic changes follow, with varying latency, the events of primary ionization and activated chemical reactions. The causal relationship between the physical (direct) and biochemical (indirect) processes on one side and the biologic consequences on the other is unknown; moreover, radiation effects on critical enzyme systems or tissue metabolism have not as yet been demonstrated at times when incipient structural changes of eye tissues have clearly developed. At present, then, morphologic studies on a cellular level provide information on the earliest radiation-induced injury at a time when biochemical investigations fail to do so.

Because of clinical implications, as well as suitability for controlled cytologic analysis, systematic work on early lesions of ocular tissues resulting from exposure to ionizing radiations has been carried out most extensively on the lens.

In this presentation, the results of light microscopic and electron microscopic investigations of incipient cellular changes will be compared. The initial microscopically discernible signs of cell injury that follow exposure of the eye to a dose of about 1500 r x-rays or smaller doses of high energy particles occur with the brief latency of about 10 minutes. At this time the number of prophases in the epithelium is already decreased and 20 minutes later it approaches the zero level. Metaphases and telophases show subsequently a progressive reduction in counts. At a dose level of 1000 to 1500 r x-rays, the mitotic activity reaches zero about 50 minutes after irradiation.

The brief latency of the biologic effect has been explained as the time required for interaction of physical with biochemical factors and, in addition, as the time necessary for the development of visible signs of biologic damage. The duration of mitotic suppression is dose dependent. After exposure to 100 r, dividing cells are absent for 4 days. The inhibition lasts 6 days when the dose is doubled. The time required for recovery to a normal level of cell division also depends on the dose, as does the extent of the subsequent overcompensating increase in mitotic cell counts.

Of greater cytopathologic significance than the effects on mitosis are the early signs of injury to cell constituents seen under the light microscope. They consist of clumping of chromatin and extrusion of globular Feulgen-positive substance from the nucleus into the cytoplasm, and later into the extracellular space. The number of injured cell nuclei increases with the dose up to 1000 r x-rays. Beyond this, it seems that a saturation level is reached, since the use of 2000 r x-rays does not result in a further rise in the number of degenerate cells. A number of damaged cells undergo complete destruction, which is reflected in a relative sparseness of the cell population of the germinative zone in later stages. Other nuclei apparently suffer only small losses of chromatin substance.

Such cells may recover, survive, divide, and differentiate. It is possible, however, that their daughter cells of the next or later generations may not develop to healthy fibers, which in turn could produce cataractous changes after long periods of time.

As a rule, the signs of damage to the cytoplasm are not visible with the light microscope within three weeks after radiation with a medium dose of x-rays. This apparent discrepancy in the onset of nuclear and cytoplasmic changes vanishes when the material is subjected to electron microscopic examination. In fact, the many radiation-induced changes visible under the electron microscope make it necessary to correct the generally held opinion of a primary change of the cell nucleus followed by relatively late damage to the cytoplasm.

Since practical applications of exposure to ionizing radiations, rather than academic considerations of radiobiologic problems, are expected in this discussion, the question arises, what inference can be drawn from observations of early cytopathologic events during radiotherapeutic procedures or accidental exposure of the eye to ionizing radiations? Evidently, such radiations applied in a sufficiently high dose produce immediate and, as a rule, irrevocable changes in lens tissue which may lead to cataract formation, although other ocular tissues

escape signs of permanent damage. The long latency of clinical signs of this damage should not create a feeling of undue security in radiotherapeutic procedures. Knowing the sequence of events on a cytologic level, one wonders whether the indications for radiation therapy, particularly of non-neoplastic ocular diseases, should not be critically re-evaluated. In any case, some comprehension of the dose dependency of radiation injury and of the relative sensitivity of the various zones of the lens epithelium is essential for the treatment of eye tissue with ionizing radiations. Without a knowledge of these facts, the serious complication of a therapeutically produced radiation cataract is unavoidable.

Radiotherapy of Lesions of the Orbit and Ocular Adnexa

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The principal role of radiotherapy in ophthalmology is in the treatment of malignant neoplasms. In this field radiotherapy often equals surgery as a curative method. The indications for its use are well defined and it should be employed only when the nature of the disease is known and the effectiveness of radiotherapy in its treatment has been demonstrated. Benign processes in general are not radiosensitive and should not be treated with radiation. Neoplasms which are known by experience to be insensitive to irradiation or incurable by radiotherapy should be given such treatment only in exceptional circumstances.

In the treatment of early carcinoma of the eyelid (either basal or squamous cell), radiotherapy finds its greatest area of usefulness. These tumors are essentially skin cancers; in theory they should be controlled with almost complete certainty, though in practice only about 90 per cent are effectively controlled. The argument for radiotherapy is that by its use the disease can be controlled with almost no residual cosmetic defect or disability. When the tumor is more advanced and tissues have been destroyed, control by radiotherapy is still equally likely, but the defect is more pronounced. Although destroyed tissues cannot be replaced, the result is usually not unacceptable and certainly the period of disability is less than that required for reconstructive surgery after surgical removal.

When the disease involves the inner canthus and surgical removal would mean either plastic repair or damage to the lacrimal duct, radiotherapy can often effect both a good functional and a good cosmetic result with control of the disease equal to that produced by a surgical operation. When canthal lesions are fixed to the bone, however, radiotherapy may, in general, be said to be less desirable than surgical removal.

When the tumor is longstanding, neglected, or recurrent, or when it has invaded the orbit, fixed the globe, or extended widely into the soft tissues about the globe, the ideal treatment is exenteration. Control by radiation therapy under these circumstances is uncommon—about 25 per cent. Adenocarcinomas, nevocarcinomas, and melanomas in general may be considered to be radioresistant, and radiotherapy should be used only when curative surgical procedures cannot be offered or will not be accepted.

In the treatment of pituitary tumors, a few of the lipohistiocytoses, and malignant lymphomas, as in that of early and noninvasive epithelial neoplasms of the lid, radiotherapy is to be preferred to other methods of management. In most other conditions, however, radiotherapy is either ineffective or useful only in the palliation of incurable and recurrent disease.

Radiotherapy of Ocular Lesions by X-Rays and Gamma Rays

Arnold W. Forrest

New York, New York

Ionizing electromagnetic rays are available in a spectrum which permits effective penetration to be limited to the most superficial layers or to reach the deepest parts of the eyes. For a given amount of ionizing radiation in tissue, the biologic effect is independent of the source. The clinical results are related only to the distribution of this radiation in the tissue.

Radiation treatment may be given for superficial lesions involving the cornea, conjunctiva, and sclera, for deep anterior segment lesions, and for deep intraocular lesions. The prime problem in dealing with superficial lesions is to deliver an effective dose to the lesion without exposing the lens equator to a cataractogenic dose. In a single exposure as little as 200 r (tissue dose) has produced a cataract, while in protracted therapy in periods between three weeks and three months, up to 1000 r has been given without cataract formation. An average figure of 500 r is accepted as the cataractogenic threshold. Radiation therapy has been used in almost every superficial ocular lesion for which other specific therapy is not available, but those in which it is most successful are phlyctenular keratitis and conjunctivitis, recurrent pterygium, vascularization of the cornea, ulcers of the cornea, carcinoma of the limbus, leproma, precancerous melanosis of the conjunctiva, and nodular episcleritis.

Deep anterior segment lesions, *i.e.*, those contained within the corneosclera and involving the anterior segments, include lesions of the anterior chamber and the iris. However, the lens is relatively radiosensitive and since safe radiation of surrounding areas depends on differential radioresistance or favorable distance relationships to the source of the beam, it is impossible to radiate close to the lens effectively without producing radiation cataracts. Consequently, the anterior

chamber and iris can be treated only in patients with aphakia, or with cataracts, or when a possible cataract is a relatively acceptable complication.

Among the deep intraocular lesions, retinoblastoma is the condition in which radiotherapy offers its greatest service to ophthalmology. In unilateral disease, at present, any treatment other than enucleation is only rarely indicated. In about 25 per cent of the patients, however, the disease is bilateral. In these cases, after enucleation of the eye with the more advanced disease, radiation may be given to the second eye. This treatment has been given by γ-rays of radium and Co^{60} and radon seeds and radioactive tantalum (Ta^{182}) and roentgen rays ranging from low to orthovoltage to supervoltage of the betatron. More recently, an adjuvant in the form of a radiomimetic drug, namely, triethylene melamine or TEM, has been used. Radiation alone may cure retinoblastoma but TEM is not known to do so. The two seem to be synergistic or supplementary.

Other lesions for which radiotherapy has been used with or without success are Von Hippel's disease, Coats' disease, metastatic tumor of the choroid, neovascularization of the retina and vitreous hemorrhage, uveitis, retinal vein thrombosis, sympathetic ophthalmia, hemorrhagic glaucoma, and absolute glaucoma.

Occular Therapy with Beta Particles

James E. McDonald

Chicago, Illinois

Fred M. Wilson

Indianapolis, Indiana

Few types of therapy in ophthalmology have enjoyed more undeserved praise or have received more unjust condemnation than β-radiation. In their contribution, the authors presented an evaluation of the results obtained in 694 eyes treated with β-radiation and an attempt to establish new, or confirm old, indications and contraindications for β-radiation in the treatment of certain ocular conditions.

About 60 per cent of the patients were treated with radon, the remaining 40 per cent with radioactive strontium (Sr^{90}). Clinical and experimental studies confirm the essential similarity in the therapeutic results and frequency of complications from the two sources. The results of the survey indicate that the β-particles produce effects on ocular tissue which are more or less predictable in incidence and latency. β-Radiation therapy is effective in treating corneal vascularization, especially that occurring in rosacea keratitis. It is of value as an adjunct to surgical procedures in the treatment of recurrent pterygiums. It is

especially indicated in limbal tumors with or without associated surgical excision. It seems to have some usefulness in inflammation and allergic conditions of the cornea and also in certain lid conditions. Among its undesirable effects are various complications, such as lens opacities, postradiation vessels, and interference with wound healing.

In general, because of its narrow margin of safety, β-radiation should be used only in those conditions for which it is superior to other forms of treatment, or in which other treatment has failed. In all cases, its side effects and destructive nature demand the most careful and conservative selection of clinical indications before β-irradiation of the eye is decided on.

Radiotherapy Compared to Other Forms of Ocular Therapy

William F. Hughes

Chicago, Illinois

From the reports of the other contributors, it seems that there are specific indications for curative therapy. With increasing knowledge of the tolerance of the ocular tissues for radiation, treatment can be administered in dosage sufficient to effect cures without undue damage to the normal tissues, rather than in timid homeopathic doses or for palliative effects only. As Dr. Schulz stated, "Radiotherapy is not a means of improving the results of unwisely chosen and poorly executed surgical removal, nor should surgical procedures be used by the radiotherapist habitually as a cleaning up device." Because of the possibility of late complications if excessive radiotherapy has been used, it should be reserved for the conditions in which it is definitely superior to other methods of treatment or in which other methods have failed, especially in cases involving the treatment of nonmalignant lesions.

Comment: To write a comment to an abstract of the material presented in this symposium would be, to say the least, presumptuous. Experts on the ocular effects of ionizing radiation and on ocular radiotherapy have given us all that they were permitted to give us in their allotted times and the comments to their outstanding presentation was in fact given in advance by the symposium's moderator, David Cogan. Surely, Dr. Cogan made an understatement when asserting that the panel discussed "*Some* Specific Aspects of *Possible* Interest to *Some* Ophthalmologists." They covered *many* aspects (as many as they could) and which, no doubt, are of *very great* (unavoidably great) interest to *all* of us.

Arthur Linksz

THE RIGIDITY OF THE NORMAL HUMAN EYE

E. Prijot and R. Weekers

Liege, Beigium

Ophthalmologica, 1959, *138:* 1–9

From studies by several authors, Friedenwald in 1937 estimated that when intraocular pressure was above 5 mm. Hg, the relationship between the modification of intraocular volume and the logarithm of the pressure is linear and can be expressed by the formula:

$$\log \frac{P_2}{P_1} = KV$$

if P_1 is the initial intraocular pressure, P_2 the final pressure, V the change in the volume of the globe, and K a constant which Friedenwald calls "the coefficient of ocular rigidity.

Recent studies have questioned the constancy of the coefficient of rigidity. Recently McBain pointed out that sources of error existed in certain studies and considered that the problem could be solved only by direct measurement of the rigidity of the eye in place as influenced by introduction of fluid into the globe. So far this has not been done with fully adequate instruments for taking the measurements. We recently had to enucleate two eyes during exenteration of the orbit for neoplasm which made it possible to measure ocular rigidity with the eye in its normal place.

The apparatus was composed of the following parts: (a) a system for introduction of compressed air under known and stable pressure; (b) an electronic manometer connected by means of a feed and control apparatus to a recording potentiometer; (c) a Dallemagnes ultramicroburette.

Two hypodermic needles were introduced into the anterior chamber. One was connected by a polyethylene tube to both the ultramicroburette and the manometric system, which was regulated to a pressure level the same as the intraocular pressure of the eye. The other was connected by an identical tube to the electronic manometer connected with the recording apparatus. The disk of the ultramicroburette was adjusted to avoid producing hypotension.

The experiment consisted in injecting repeatedly 10 mm. of liquid and registering the successive pressures following the increase in intraocular volume. Preliminary study showed that the portion of the fluid actually entering the eye could be expressed as:

$$V = 10 \text{ mm.}^3 - 0.126(P_2 - P_1) \text{ mm.}^3$$

if V is the change in intraocular volume, P_1 the initial pressure, and P_2 the final pressure. Initial pressure was read directly on the recording apparatus, and pressure following injection after 1 to 1½ seconds.

Tabulation of measurements taken at between 20 mm. Hg and 70 mm. Hg

showed only minimal variation in ocular rigidity, and also showed that changes in ocular pressure could not be related to the coefficient of rigidity.

Comparision of results from this method with coefficients of rigidity determined by various types of tonometry showed that the latter were consistently higher. Differential tonometry does not take into account the corneal indentation caused by displacement of the fluid, which is apparently associated with a deformation of the posterior pole of the globe. For these reasons, tonometry underestimates the volume of fluid associated with the elevation of ocular tonus, which leads in turn to overestimation of the coefficient of ocular rigidity. These studies confirm Friedenwald's observations.

Comment: This excellent study provides the first cannulation estimates of scleral rigidity in the living human eye. The finding that scleral rigidity remains constant with considerable changes in intraocular pressure confirms the log relationship of pressure and volume postulated by Friedenwald. This confirmation has been particularly needed in view of recent studies on animals and enucleated human eyes.

The actual value of the scleral rigidity coefficient obtained is remarkably low and lower than tonometric estimates on the same two eyes. The low coefficient suggests to the authors that there is a difference in the deformation of the posterior pole of the eye *in situ* from that which is obtained *in vitro*. It is clear that much more work of this nature is needed both from the point of view of estimation of scleral rigidity and for more accurate calibration of tonometers.

BERNARD BECKER

FURTHER OBSERVATIONS ON THE APPEARANCE OF FLUORESCEIN IN THE RABBIT EYE AFTER INTRAVENOUS INJECTION

LENNART BERGGREN

Pharmacological Institute of the University of Uppsala, Sweden

Acta ophth., 1959, *37:* 215–218

Following intravenous injection of fluorescein a green cloud appears in the pupil after a certain time. This appearance time has been used in determinations of the flow of aqueous humor. In order to give a true index of aqueous flow the fluorescein cloud should originate in the posterior chamber.

Study under ultraviolet light of sections from rabbit eyes frozen at different intervals after an intravenous fluorescein injection demonstrate that a "cloud" in the pupil can originate from either the anterior or posterior chamber. Albino and pigmented rabbits have been studied to determine if there may be a strain difference with respect to this property. In pigmented rabbits diffusion from the vessels of the anterior surface of the iris appeared later than in the albino rabbits. It should perhaps also be mentioned that in the pigmented group, where the

animals showed different degrees of pigmentation, the diffusion from the vessels of the anterior surface of the iris appeared latest in the completely black rabbits. If one selected a suitable strain of rabbits it might perhaps be possible to use the appearance time as a measure of the aqueous flow provided the appearance ime was less than 2 minutes. A study of appearance and diffusion times also suggests that in situations of decreased aqueous flow (for instance in experiments with carbonic anhydrase inhibitors) a prolongation of the appearance time would occur into that period when diffusion of dye becomes manifest. Thus a large source of error will be introduced into the determination of appearance time as long as it is not possible to differentiate between the flow from the posterior chamber and diffusion into the anterior chamber.

After longer intervals the anterior chamber was often diffusely filled with green fluorescence.

Comment: This paper illustrates the sources of error and inadequacies of the appearance time of fluorescein as a measure of aqueous flow in rabbits. Entry into the anterior chamber by diffusion from iris vessels constitutes the major difficulty. Fortunately in the pigmented rabbit and in human eyes this source of error is of much less significance. The method still remains an extremely crude one.

BERNARD BECKER-

PHARMACOLOGY

THE INITIAL DROP OF THE INTRAOCULAR PRESSURE FOLLOWING INTRAVENOUS ADMINISTRATION OF ACETAZOLAMIDE IN MAN

ERIK LINNÉR AND PER WISTRAND

Department of Ophthalmology, University of Gothenburg, Department of Pharmacology, University of Uppsala, Sweden

Acta ophth., 1959, *37:* 209–214

The initial drop of the intraocular pressure following an intravenous administration of acetazolamide (a carbonic anhydrase inhibitor) in man has not been previously studied. Although in the sheep no measurable pressure drop was observed within 60 minutes, a drop of intraocular pressure has been reported within 2 to 3 minutes in the rabbit, cat and dog. The sheep and the human eye fall within the same category; each has excess of chloride and a deficit of bicarbonate.

Healthy human subjects, aged 20 to 30 years, with normal eyes and three patients with suspected chronic simple glaucoma, without treatment, were studied in the investigation on the speed with which the eye pressure response to carbonic anhydrase inhibition occurs in the human eye.

The subjects were examined twice with an interval of 1 to 3 days. At first examination, one subject received acetazolamide and the next subject was not given the drug; at second examination each subject received the opposite treatment. The intraocular pressures and the tonographic tracings were obtained after topical anesthesia. For intermittent pressure readings the tonometer was applied for at most 10 seconds. Examinations were made between noon and 4 p.m., and between 1 and 4 a.m. after sleep.

The drop in the intraocular pressure started in 2 minutes after intravenous injection of acetazolamide, 5 mg. per kg.; 24 hours later the pressure returned to normal values. The pressure drop at night after corresponding administration resembles that of day time but seems to start a little later.

No regular and significant pressure drop was seen after the injection of acetazolamide. A clear pressure drop was also not found in similar experiments in three cases of suspected chronic simple glaucoma. Some side-effects after injection were noted, such as flatness of taste when beverages containing carbon dioxide were taken, slight numbness, tingling, and an acute heavy feeling in the occipital region.

Acetazolamide caused no regular and significant pressure drop when the tonometer was kept on the eye continuously but a significant drop was observed when it was applied intermittently; this discrepancy deserves further study. Characteristics of the eye pressure response following carbonic anhydrase in-

hibition are similar despite species differences in the composition of the aqueous humor.

Comment: This report confirms the rapid effects of intravenous acetazolamide on intraocular pressure in man. The interesting observation is made that acetazolamide does not produce a dramatic change in the shape of the tonogram. This is interpreted as a failure of acetazolamide to significantly alter intraocular pressure in the eye with the tonometer in place. It is easy to demonstrate that the calculated effect of decreasing flow by 50 per cent during a tonogram does not change the shape of the tracing dramatically, but rather increases the slope only very slightly.

The authors' tracings can be used to determine the excessive "loss" of fluid from the eye following Diamox administration (*i.e.*, excess of ΔV over that calculated for the latter part of the tonogram). In this fashion crude measurements of the decrease in rate of entry of fluid into the eye can be made. Following Diamox one gets estimates of 40 to 60 per cent inhibition of aqueous secretion.

BERNARD BECKER

Miscellany

HISTORY

DOCTORS AFIELD

L. L. Zamenhof: Dr. Esperanto

E. James Lieberman

Massachusetts Mental Health Center, Boston, Massachusetts

New England J. Med., 1959, *261:* 963–965

Ludvig Zamenhof (1859–1917), the ophthalmologist who invented Esperanto, was born 100 years ago in Bialystok, Poland, and practiced his specialty in one of the poor districts in Warsaw. The idea of a universal language fascinated him while in high school, and at the age of 19, just before he enrolled in the University of Moscow Medical School, he had not only developed Esperanto but produced original works in the new tongue, including poetry and songs. After receiving his medical degree in 1885, he studied ophthalmology in Vienna and Warsaw. In 1887, his *Lingvo Internacia* was published in Russian, Polish, German, French and English editions under a pseudonym, Dr. Esperanto, as he feared his practice would suffer if his avocational pursuit were known. Soon letters deluged him about what henceforth would be known as Esperanto. Since 1889 successive monthly journals in Esperanto have appeared; that now current is the flourishing *Esperanto Review Internacio.* In 1905 the first congress of 800 Esperantists from 30 countries met in Boulogne; a second congress met in Geneva in 1906. At the third congress in Cambridge, England, in 1907 there were 1500 Esperantists. Esperanto has won the approval of the French Academy of Sciences, the League of Nations, the International Red Cross and UNESCO. For blind people everywhere there are Braille books in Esperanto. Zamenhof was skilled in 19 languages; during his isolation in World War I, he completed his translation of the Bible from the Hebrew into Esperanto. Because of his Jewish background, Zamenhof at first leaned towards Zionism but his later thoughts shifted to a concept of a world that transcended all nationalism.

Comment: Other ophthalmologists besides Zamenhof have achieved fame through their side interests, including Conan Doyle and one of the popes. Since Latin ceased to be the universal language of science, scientists have had to be conversant with English, French, German, Spanish, Italian and now also Russian. Other universal languages have been invented for auxiliary purposes, but Esperanto is the only one that has achieved

some measure of success. Zamenhof based his vocabulary on the most common European roots, his grammar on English, and he made different words from one root by prefixes and suffixes as is done in Polish. Like many logical and desirable ideas, such as the 13-month year, simplified spelling and the universal use of the metric system, a universal language remains more of a hope than a reality. The State of Israel, which urgently required a universal language for its polyglot population, chose modernized Hebrew. Would that it had been Esperanto!

JAMES E. LEBENSOHN

This is the Barnes Hospital Group as seen from Forest Park, At the far right is McMillan Hospital and atop it, the Oscar Johnson Institute, rising to a total of thirteen stories. At present this group of hospitals provide approximately 1000 beds.

Visits

Visit to The Department of Ophthalmology, University of Washington School of Medicine

The McMillan Hospital houses the Department of Ophthalmology, an autonomous but integrated part of the medical school and general hospital program; its consultation, teaching, and research facilities keep it a constant partner of the other specialties and disciplines of the medical center. There are over 28,000 patient-visits a year to the Eye Clinic.

THE Department of Ophthalmology of Washington University School of Medicine is dedicated to research and to the training of teachers and investigators. The members of the full time staff have each developed proficiency in specialized clinical and research areas. In addition to rendering more expert service to the patient and his referring physicians, an important stimulus to research is provided by the clinical problems presented. This setting offers opportunities for rapid application of research findings to the patient's problem. It also affords highly qualified teachers, an ample supply of referred teaching material, and an attitude conducive to the training of astute clinicians and academicians.

Training is not only provided in the various phases of both routine and also more highly specialized aspects of clinical ophthalmology, but also special efforts are made to stimulate research interests and develop critical inquiring attitudes among the trainees. This is approached by providing the time, the facilities, the background, the advice and the assistance for research activities. Much of the clinical teaching is "bedside" and patient orientated. The residency program is designed not as a mere service function, but as an educational experience initiating a long-term program of critical appraisal and continued self-education. In addition opportunities are afforded during the training program for teaching at a medical student level, as well as at postgraduate, grand rounds, and seminar levels. All of these efforts are subject to critical appraisal by teachers and fellow trainees in a "give and take" atmosphere. Emphasis is placed on clear thinking and the ability to question, verify, or disprove written or spoken dogma on the basis of sound data.

The following photographic visit to the department is a result of efforts of one of the trainees. It attempts to portray how the basic purposes and ideals of the department are made functional in terms of physical facilities, teaching methods, and personnel.

Bedside and clinic rounds emphasize learning on a case-at-hand basis. A spirit of inquiry pervades rounds just as it does seminars and other teaching functions of the department. Clinical or laboratory research is often stimulated by a critical appraisal of the problems presented by the patients. Every effort is made to question dogma not backed by data. Work rounds are conducted daily by the Chief Resident, and there are scheduled rounds three times a week by full-time and visiting staff members. Still more informal and personal teaching occurs on small unscheduled rounds. Didactic teaching, although de-emphasized, balances the program by lectures in the basic sciences of ophthalmology (4 hours per week). Weekly Friday night two-hour seminars are conducted by members of the staff, residents, or distinguished visitors. Monday noon seminars are devoted to preliminary reports on research in progress. Increasing emphasis is placed upon residents preparing and conducting seminars.

In a program devoted to learning by doing under supervision, intensive personal instruction is especially essential early in training. Complete work-ups are emphasized from the beginning of the residency. This makes for very personal and flexible teaching, tailored to the needs of the individual. It places a heavy teaching burden on senior residents and staff, but results in a rapid attainment of proficiency and confidence balanced by a desire for instructive consultation.

The clinic area is in the process of being remodeled. The Low-Vision Clinic shown here is serving as a guide to the design of the new offices for the residents and full-time staff. Teamwork is emphasized in all clinic activities: in this clinic the coordinated efforts of staff men, social workers, and residents are utilized to obtain maximum benefit to the patient, instruction for the resident, and an evaluation of the efficacy of optical aids.

Special clinic divisions, such as the glaucoma, retinal, and muscle clinics afford concentrations of patient material for optimal experience, for teaching, for maximal benefit to the patient, as well as for special studies and research. Modified euthyscopic techniques are being demonstrated to a student orthoptist by Dr. Lisa Cibis.

The clinic offers complete services to its patients, including an efficient and economical optical shop. By being in the clinic area itself, residents are afforded the opportunity to learn dispensing techniques and problems.

Left. Residents assist with private surgery during a three-month period in their second year, and while assigned to this service they do complete eye work-ups and make daily dressing rounds on all private patients (about 2,000 per year).

Below. A corneal transplant operation as performed by the Chief Resident is filmed for presentation on television. A very effective quarter-hour program was presented and well received by the public. It served to explain the functions and needs of the Washington University Eye Bank. The eye bank processed over 800 eyes last year and provided donor material for several other hospitals and eye banks throughout the country. Eyes were also used for research and teaching. After use or preservation of the corneas for transplants and the vitreous for retinal detachments, all were subjected to routine gross and microscopic study by the pathology resident. Many of the patients had been thoroughly studied and fundus photographs made before death. In these eyes careful histologic studies were made of any lesions recorded previously and compared with *in vivo* findings. Complete autopsy examinations were available on most of the donors for correlation of ocular and systemic pathology.

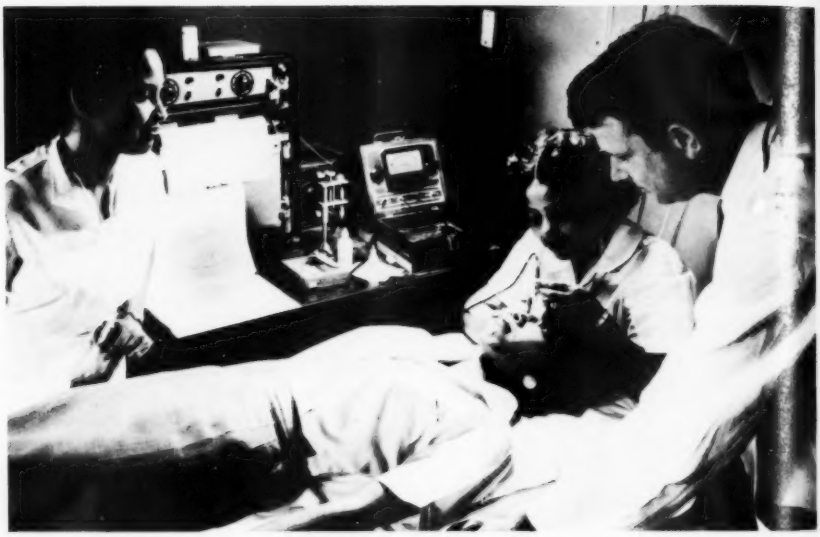
Ward surgical material continued to be abundant, amounting to some 900 cases last year. All ward surgery is done by the residents, with the more complicated cases operated upon by the Chief Resident.

Above. One of the most profitable experiences in the residency is the three months in the second year spent on the Consultation Service. All patients in the hospital group with ophthalmic problems can be seen by him. The large variety of interesting and often unusual medical and especially neurological material make it richly rewarding. Interesting fundi are photographed with the hand fundus camera (shown in the photograph), developed by one of the research fellows of the department, Dr. Satoshi Noyori. An important rapport is established between eye and other resident services. A knowledge of interesting cases in the 1000-bed center is used to provide inspirational teaching material for medical students. This undergraduate teaching program has rapidly become one of the most popular in the medical school.

Right. Specialization by members of the full-time staff is exemplified here in Dr. Paul Cibis' (Associate Professor of Ophthalmology) retinal service. A unique training opportunity is offered for all residents and selected fellows in the diagnosis (including accurate fundus drawings) and treatment of detachments as well as other retinal disease processes. The most advanced techniques are practiced, including photocoagulation in favorable cases. The patient load is very heavy in this clinic.

The department has its own pathology laboratory. All residents rotate through this service in both their first and second years of training. In the upper photograph, the prior week's material is reviewed under the guidance of eye pathologists, Drs. Albert Ley (Assistant Professor of Ophthalmology) and Ted Sanders (Associate Professor). Others in the photograph include the eye residents (who have already prepared their impressions of the material) and a resident from the general surgical pathology service in Barnes Hospital.

In the lower picture the most interesting slides are being presented by the second year resident at the weekly pathology conference, one of the most interesting and best attended of the many teaching sessions. Recently this conference has been moved to the auditorium in order to accommodate the large number of people attending regularly.

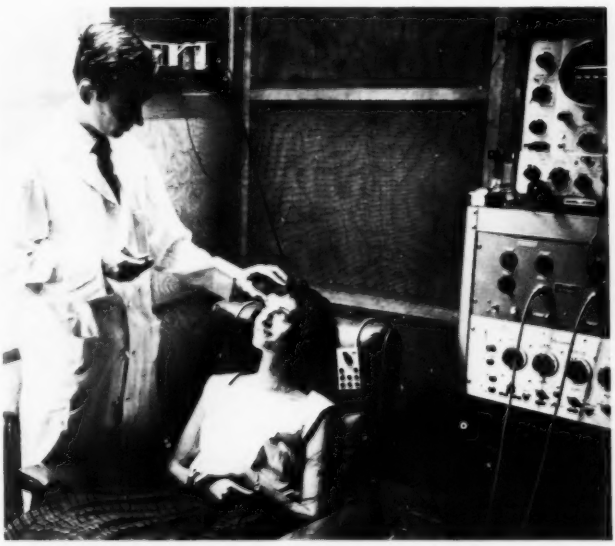


Above. The department has a large collection of tonograms (over 40,000) on patients referred for diagnosis and evaluation of therapy of glaucoma, complete with histories. Presently about 300 tonograms are done each week including clinical, research, and "family plan" patients. Opportunities are available for current clinical as well as retrospective research.

Below. Clinical tonograms are read each week by Dr. Bernard Becker (Professor of Ophthalmology, and reports including suggestions for therapy are sent to the referring physicians. Also reported are the results of ancillary tests available without charge: gonioscopy and applanation tonometry with determination of scleral rigidity. During this 3- to 4- hour session informal discussions stimulated by the case reports, the tonographic findings, and questions raised by staff and the many visitors run the gamut of various aspects of glaucoma.

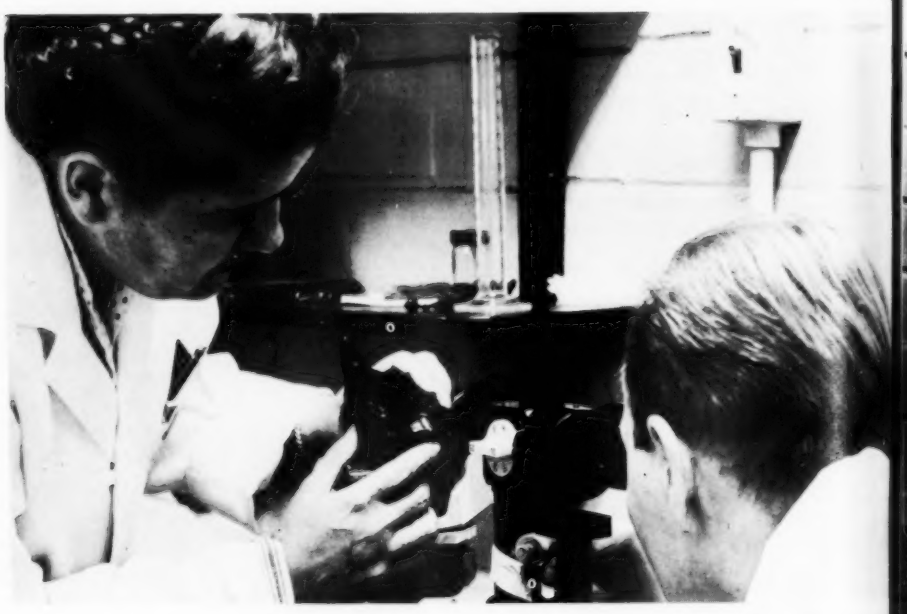
Research facilities and opportunities are offered to all residents. Most residents participate in or initiate clinical or laboratory research projects. These are reported at weekly research seminars and often prove of sufficient interest for publication or presentation at research meetings. Residents with special interests in academic careers in research and teaching may apply for NIH trainee stipends under the department's training grant. Informal conferences with members of the staff help to plan the careers of the trainees. Such trainees spend an extra year pursuing their particular research interests and are afforded additional opportunities for basic training as well as administrative and teaching responsibilities.

In the photograph, Dr. Jay Enoch (Research Assistant Professor of Ophthalmology and a Ph.D. in physiologic optics) discusses experimental data with one of the residents who has been working with him.



Dr. James Miller (Assistant Professor of Ophthalmology) subspecializes in pediatric ophthalmology, and especially strabismus. He is shown here with a part of the elaborate equipment he has assembled for studies in electromyography of extraocular muscles.

At present the department has four visiting foreign doctors at work in research. Dr. Tsuyoshi Yamashita of Tokyo, Japan, has already co-authored several papers with Dr. Cibis. Dr. Satoshi Noyori of fundus camera fame, at present is working on a euthyscope and light coagulator. Dr. Johannes Rohen, a German anatomist, has joined the team studying various aspects of the histology and function of the trabecular meshwork. Pictured is Dr. Ake Holmberg of Uppsala, Sweden, who is continuing his electron microscopy studies of the ciliary epithelium, and has recently added brilliantly to our knowledge of the ultrastructure of the outflow channels. During his 18 months in the department he has stimulated several of the residents as well as full-time staff to use the electron microscope as a research tool. Most productive have been the efforts designed to correlate the histology, histochemistry and altered physiology with the electron microscope findings.



Dr. Marguerite Constant (a Ph.D. in biochemistry and Research Associate Professor of Ophthalmology) is interested in the metabolism and requirement of the lens *in vitro*. However, she devotes much of her time to teaching and assisting residents in the design and execution of their research efforts. Her enthusiasm, versatility, and patience are responsible for much of the interest in research expressed by the residents. Typically, she is shown here assisting a resident in the slit lamp examination of a cat in the animal operating room.

Dr. Robert Moses (Assistant Professor of Ophthalmology) has just returned from a year's work at Bern, Switzerland with Dr. Goldmann. Here he is seen reviewing some recent data on the role of the scleral rigidity coefficient in clinical tonometry and tonography.

Dr. Bernard Wortman (Research Assistant Professor of Ophthalmology and our other full-time biochemist) observes the operation of automatic radioactive counting equipment by one of the residents. A large program on aqueous humor dynamics is in progress. Research is also carried out on many other aspects of ophthalmology and related fields (glaucoma, lens culture, experimental retinal pathology, experimental zonulysis, mucopolysaccharide metabolism, tissue culture of ciliary body, enzymatic histochemistry, hypothermia, carbonic anhydrase inhibition, etc.).

A staff man and resident are found here in the 12th floor departmental library at night. Here volumes and journals, which duplicate the medical library's items pertinent to the clinical and research needs of the department, are available to the staff at all times.

At the end of a full day, one of the residents relaxes in his quarters on the 12th floor of McMillan Hospital.

Announcements

EMORY UNIVERSITY

postgraduate training program

TECHNIQUES IN OPHTHALMIC SURGERY

will be presented on December 1 and 2, 1960, at the Grady Memorial Hospital, Atlanta, Georgia, under the sponsorship of the Grady Clay Memorial Eye Clinic and the Department of Ophthalmology of Emory University School of Medicine.

The course is designed for the practicing clinical ophthalmologist and will consist of lectures and panel discussions by such outstanding national authorities as Dr. Frank Costenbader, Chairman, Department of Ophthalmology, Children's Hospital, Washington, D. C.; Dr. John McLean, Professor of Ophthalmology, Cornell University School of Medicine, New York; and Dr. Harold Scheie, Professor of Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Diagnostic principles and techniques, preoperative and postoperative management, and surgical principles and techniques in extraocular muscle surgery, cataract surgery, and glaucoma surgery will be discussed by these distinguished surgeons. Please plan now to attend the meeting.

F. PHINIZY CALHOUN, JR., M.D.
Chairman, Department of Ophthalmology
J. J. STOKES, M.D.
Director, Postgraduate Education
Department of Ophthalmology

Postgraduate Training Program

UNIVERSITY OF MICHIGAN

Supported by a grant from the National Institutes of Health, the Departments of Physiology, Ophthalmology, Otolaryngology and Psychology of The University of Michigan join in offering postgraduate training to qualified individuals desiring further research and teaching experience to prepare themselves for independent careers in science.

STAFF

Mathew Alpern, Ph.D.
Associate Professor of Ophthalmology, Psychology and Physiology

Robert W. Doty, Ph.D.
Associate Professor of Physiology

Merle Lawrence, Ph.D.
Professor of Otolaryngology, Psychology and Physiology

Those interested in joining this program should write to:

Dr. Robert W. Doty, Department of Physiology
The University of Michigan, Ann Arbor, Michigan

physiology of sensory system

Emphasis is upon the physiology of sensation, approached through neurophysiology, neuroanatomy, psychophysics and studies of animal behavior. Trainees are encouraged both to develop experimental approaches of their own and to work with a senior staff member on experiments already in progress.

In addition to research endeavors and part-time teaching of physiology, trainees may take any or all of the following special courses:

Electronic Instrumentation in the Biological Sciences. K. E. Bignall
Advanced Laboratory in Sensory Physiology. Staff.
Advanced Neurophysiology. R. W. Doty
Physiology of Vision. M. Alpern
Theories of Hearing. M. Lawrence
Sound Conduction in the Ear. M. Lawrence
Developmental and Microscopic Anatomy of the Temporal Bone. M. Lawrence

Trainees must have an M.D. or Ph.D. degree or equivalent, an enduring interest in research, and an outstanding record of scholastic and intellectual attainment. U. S. citizens or those who have filed a declaration of intent are eligible for training stipends at the following rates, of which $300 per month for a total of 36 months is customarily considered tax exempt.

Postdoctoral year	Yearly Stipend
First	$4500
Second	5000
Third	5500

An additional $500 per year is allowed for each dependent.

Current Review

CORNEAL WOUND HEALING

A Review of Recent Literature

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EARLY COMPONENTS OF CORNEAL WOUND CLOSURE

Immediate responses of the cornea to wounding are mostly mechanical, mediated by release of stresses within the corneal structure. The elastic Descemet's membrane retracts together with the posterior stroma producing a wide inverted V-shaped wound gaping posteriorly. The anterior layers retract much less.

At the wound edge the stroma becomes 1½ to 2 times thicker than normal. This occurs within 1 or 2 minutes and indicates elastic separation of fibers rather than edema, which later may produce this effect.

As early as 3 to 10 minutes, a fibrin plug fills the wound, and extends into the conjunctival sac and into the anterior chamber. The shape of the wound keeps the fibrin "cork" wedged in the wound, thereby sealing it and permitting reformation of the anterior chamber, unless the wound is widely separated by inadequate suturing or struggling of the individual. This fibrin is believed to be derived from the secondary aqueous, as evidenced by its presence after posterior incision and its absence after anterior incision of the cornea. It has little appreciable adhesive action, but acts as a plug and as the framework for later fibroblastic activity. Edema of the cornea develops slowly during the first hour and has little importance in producing coaptation of the edges of the wound during this period.[1]

Epithelium migrates over the wound anteriorly within the first hour with some mitosis in the adjacent epithelium. Cell division apparently plays a minor role in the process.[2] These conclusions were found by McDonald[1] with the slit lamp and histologic techniques in corneal incisions of rabbits, cats, dogs, monkeys, and human beings. The amount of fibrin seemed greater in the secondary aqueous of rabbits than in the other species studied.

Histologically, the fibrin plug seems to block the downgrowth of epithelium into the wound.

Prior heparinization of the animals totally prevented the fibrin plug formation leaving the wound agape and the anterior chamber flat.

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McDonald[1] also states that indiscriminate washing of the anterior chamber during cataract surgery removed the fibrin in the secondary aqueous which led to an open wound, flat chamber, and possible prolapse of intraocular tissue.

Dunnington and Regan's[3-5] studies on Rhesus monkeys showed a well developed anterior epithelial plug by the end of the second postoperative day in corneal sections, and a fibrinous one in limbal incisions with a conjunctival flap. Fibroblastic proliferation, which was well established by the 4th to 5th day, progressed most rapidly in the anterior part of the wound. At the end of 14 days there was often posterior gaping of the wounds.

Bowman's membrane is not regenerated, but is replaced by epithelium. Dunnington and Smelzer[6] in another study used S^{35} in rabbits. This isotope is incorporated almost exclusively in the mucopolysaccharide component of connective tissue which comprises most of the stroma. Normal corneas showed glycogen filled epithelium covering the wound completely in 24 hours. Few polymorphonuclear leukocytes were seen at 24 to 48 hours; fewer at 7 days. Enlarged keratoblasts were seen along wound margins at 48 hours, when radioactive sulfate was being laid down at the wound edge at a greater than normal rate. Thus, synthesis of sulfated mucopolysaccharides is the first sign of new connective tissue formation, preceding by a short interval the first appearance of reticular fibers. This may begin as early as 17 to 24 hours after injury. This is correlated with the appearance of enlarged stromal cells at the wound edge.[7]

Healing, indicated by reticular fiber formation, was well begun in all cases by the 5th day. From the 7th to 15th day healing progressed steadily without change, and a few lymphocytes were observed. By 15 days parallel bands of connective tissue (cornea style) were seen; before, they were not oriented in any one direction. At 45 days wound repair was still noted, but greatly reduced.

The importance of endothelium to corneal transparency was pointed out by Leber in 1873. Fuchs in 1917 suggested that following injury Descemet's membrane was not completely reconstructed, but a membrane thinner than the original appeared to be secreted by endothelium.

Cogan[8] showed experimentally that endothelium heals rapidly and completely in the presence of a normal Descemet's membrane.

Morton, Ormsby and Basu[9] scarified the inner aspect of rabbit corneas and showed that in 3 hours the denuded stroma became edematous, and fibrin clots, with scattered round cells enmeshed, attached to the stroma in 6 hours. Endothelial regeneration was first seen at 24 hours which by 48 hours formed a migrating layer over the defect from the cut and retracted Descemet's membrane. Proliferation continued until a fusiform "scar" of cellular tissue covered the area of trauma. After 1 to 2 weeks, hyalinization of the scar from the stromal side toward the epithelial surface began, and lasted 3 weeks. The regenerated Descemet's membrane was in all cases present after 21 days. At 90 days the new membrane had reached its maximum thickness of about 50 per cent of the thickness of Descemet's membrane.

GENERAL CONSIDERATIONS OF WOUND HEALING

From histochemical studies, chemical analyses, and observations with the electron microscope it has been learned that much activity takes place during the so-called lag phase of wound healing. This initial period of 3 days, formerly considered to be a relatively inert one, is now regarded as an important link in the healing process, for it is during this time that the "building blocks" of repair are laid down.[10]

Most evidence supports the theory that collagen results from the interaction of intra- and extracellular substances. A reaction takes place between fibrils laid down along the cellular membrane and materials found in the ground substance.[11] Generally it is agreed that the important activating factor in the ground substance is a mucopolysaccharide.[12, 13] This matrix, once considered an inert amorphous mass, is now known to consist of tissue fluids, mucopolysaccharides, and mucoprotein complexes, and to be metabolically active. Ground substance is an optically homogeneous structure normally a gel capable of becoming a fluid.[14, 15] Its consistency varies with age, its degree of activity, and the pathologic condition of the tissue. Much of this change depends upon the polysaccharides in the ground substance. Metachromasia, the staining of tissue in a different hue from that characteristically associated with it when stained with a pure dye, may reflect some of this change.[15]

Continuous with ground substance is a so-called cement substance, a protein-carbohydrate complex, which binds together the microscopically visible fibrils. Recent investigations have shown that ground and cement substances are essentially the same, although their chemical components may vary in different parts of the body.[12, 15]

There are two schools of thought about the origin of ground substance: One believes the mucopolysaccharides of ground substances are the products of mast cells, while the other says that they are the secretory products of fibroblasts.[12, 16-20] In any case ground substance and fibroblasts are intimately associated with collagen formation. Dunphy and Udupa have summarized the current belief in these words: "The ultimate formation of collagen which provides tensile strength to a wound is dependent upon two factors: a protein component, probably produced by fibroblasts, which passes through several stages before becoming collagen; and a carbohydrate component,—a complex mucopolysaccharide produced either by mast cells or tissue cells."[21] Collagen results from the interaction of these two substances.

Dunphy and Udupa[21] have attempted to measure the sequential formation of mucopolysaccharides and collagen in abdominal wounds of rats. Their studies showed that the content of mucopolysaccharides becomes greatly increased during the early stages of repair and reaches its peak about the 5th or 6th day, at which time the chemical and histologic evidence of collagen appears. As the collagen forms, the hexosamine content of the wound decreases steadily and there is a "a remarkably good correlation between the gain in tensile strength

and the appearance of collagen." Great activity starts in the ground substance within a few hours after injury, but no gain in tensile strength occurs prior to the formation of collagen.

SPECIAL CONSIDERATIONS OF OCULAR TISSUES

The substantia propria of the cornea and the sclera consists of fibrous membranes containing collagen, a mucopolysaccharide, elastic and reticulin fibers. In the cornea the fibers are small, regularly arranged, and intimately connected with the ground substance, which is abundant and contains keratosulfate, a mucopolysaccharide found only in the cornea. It is keratosulfate, with chondroitin and chondroitin sulfate A, that makes the corneal stroma strikingly metachromatic.

On the other hand, scleral fibers vary in size, are irregularly arranged and can readily be separated from the scant ground substance.[22] The sclera contains few mucopolysaccharides, no keratosulfate and normally shows little if any metachromasia.

The limbus shares this lack of metachromasia although its fibers are more regularly arranged.[10]

In 1937 Valy Menken described leukotaxin, a polypeptide that attracts polymorphonuclear leukocytes to the injury site. Such initial reactions take place through catalytic influences of proteolytic enzymes released within the first few hours after operation.

Weimar has recent evidence that trypsin, or a similar enzyme, liberates the chemotactic substance (a polypeptide) which attracts polymorphonuclear leukocytes.[23] These cells, in turn, liberate proteolytic enzymes, while macrophages and stromal cells act as precursors of fibroblasts. By the 3rd or 4th day the ground substance is altered and fibroblasts appear. Metachromasia occurs anywhere from 1 to 12 days after injury and closely parallels the formation of collagen. "Young" collagen, apparently, is metachromatic. Both reticulin and collagen are found first near blood vessels, then in the anterior part of the wound, and later in the posterior part.

Some investigators look upon collagen as the main mechanism on which tensile strength of tissue depends.[4] However, tensile strength may depend more on a mucin-collagen combination binding together the fibrils.[24]

VARIATIONS IN THE NORMAL HEALING PROCESS

Howes has said that "the process may be interfered with more readily than it can be stimulated."[25] Any agent that interferes with (1) fibroblast formation, (2) metachromasia of ground substance, or (3) any stage of the interaction of (1) and (2) interferes with collagen formation according to Dunphy and Udupa's[21] theory. Heparin, for example, inhibits division of fibroblasts, while freezing or crushing the tissue delays metachromasia.[6]

Cortisone, in rats, 2 to 4 days after injury reduces all new connective tissue elements, especially metachromasia of the ground substance.[26]

Topical anesthetics retard epithelialization of corneal wounds. Methionine

and ascorbic acid deficient diets also depress the accumulation of mucopolysaccharides and collagen formation.[10]

Monninger[27] reports increased wound healing with the use of trypsin and chymotrypsin in topical ointment form in several cases of corneal injury, including an alkali burn which recovered 20/20 vision after catalytic debridement by these enzymes.

A prominent physiologic effect of cortisone is its suppressing influence on the response of mesenchymal tissue to trauma or other insult. Palmerton[28] showed tensile strength and fibroblastic response to be significantly reduced in healing of corneal wounds which had cortisone before 5 days postoperativly. After 5 days, when fibroblast activity was less marked, the inhibiting effect on healing was not as noticeable. The inhibition ceased promptly when cortisone was discontinued.

The last word on the effects of cortisone on corneal healing has not been written. Fink and Baras[29] claim that Palmerton's[28] work did not consider some factors, and claim that cortisone did not affect the tensile strength of rabbit corneal wounds in their series. Palmerton did not use sodium citrate in the anterior chamber to prevent aqueous clotting in the rabbit—a fibrin clot may have prevented wound edge approximation. Fink used a 7-mm. wound while Palmerton used a 5-mm. wound. Fink placed his traction sutures at the time of surgery, whereas Palmerton placed his at the time of testing. Palmerton gave his cortisone topically and subconjunctivally; Fink gave cortisone subcutaneously. Fink gave his rabbits a protein rich diet, which may alter steroid effects on healing.

Basu[30] used "Hyfercator" burns in rabbit corneas to avoid the fibrin clot caused by excessive fibrinogen in rabbit aqueous. He applied topical cortisone, hydrocortisone, prednisone, and prednisolone and nothing to the control group. There was no difference in healing in 80 per cent of the lesions. About 25 per cent of peripheral lesions became less vascularized in the steroid group than in the control group. Cortisone seemed to do this better than the other steroids used.

Thrombin, applied topically, interferes with apposition of the wound edges, thus permitting epithelial downgrowth and healing with broad fibrous cicatrices.[4]

Sutures hold the wound edges in apposition, but are otherwise not helpful to wound healing. All sutures incite a foreign body reaction. They should be small and few in number to reduce this reaction.

Tissue responses vary with the material used. Epithelium grows rapidly along the suture tract when silk is used, and may line it completely within 48 hours. Little cellular infiltration of surrounding tissues is noted during the first week, but between the 9th and 12th postoperative days marked round cell infiltration and tissue necrosis appears if the silk is not removed or extruded. If such a suture is deeply placed, the entire thickness of the cornea may become involved resulting in a weak place in the wound.

Plain gut fragments by the 3rd postoperative day, before collagen has increased the tensile strength of the wound.

Mildly chromicized 6-0 surgical gut produces little polymorphonuclear reac-

tion early, and interferes little with the normal rate of fibroblast proliferation (4th to 6th postoperative day). During the second week the presence of round cells increases and fragmentation and absorption of the suture material begins with some increase in local vascularization. Sutures too tightly placed produce distortion of wound edges and sloughing of the incarcerated tissue, which may be precursors of epithelial invasion or hyphema.[5]

Vascularized corneas heal less readily than normal corneas. A corneal peritomy sometimes aids healing by interrupting the blood supply to these vessels.[31]

Conjunctival flaps help to approximate wound edges by counter pressure to the intraocular pressure, however direct corneal wound suturing with improved needles and sutures is now preferred. Corneas lacerated too severely for suturing may be treated with a flap which protects it from abrasion of the lids and from irritants, aligns wound edges, and helps prevent loss of intraocular fluids and contents. Some surgeons use both direct suturing and conjunctival flap immediately afterward.

There are two main types of conjunctival flaps: the dissected flap, which covers the cornea with a "raw" connective tissue surface allowing fibroblastic repair of the wound in the presence of blood and serum, and the fornix flap which covers the cornea with conjunctival epithelium, allowing epithelial healing of the anterior portion of the wound. The first has the disadvantage of possible permanent adherence to the wound with leukoma formation. The latter was designed as a temporary protection for wartime eye injuries but is also useful in peacetime practice.[32]

CONCLUSIONS

Corneal injury immediately allows an inverted V-shaped wound to form which gapes posteriorly more than anteriorly, and becomes thicker than normal cornea by fanning out of stromal fibers and later by edema.

A fibrin plug is formed, in human as well as experimental animal eyes, within 3 to 10 minutes after injury. This plug seals the wound by "corking" it, not by contributing tensile strength.

Epithelium migrates over the wound anteriorly within the first hour and in 2 days fills any defect not already plugged.

Bowman's membrane is not regenerated.

Healing progresses from anterior to posterior in the stroma for more than 45 days.

The endothelium begins to migrate after 24 hours covering the posterior defect in 48 hours. It secretes a new "Descemet's" membrane after 21 days, completing the process by 90 days after injury.

A chemotactic substance is liberated by injury. This polypeptide sets in motion several mechanisms which are as yet not known. As a result polymorphonuclear leukocytes appear, proteolytic enzymes are activated, and lymphocytes, macrophages, and fibroblasts appear in the injured area.

In the presence of young fibroblasts or mast cells, the mucopolysaccharides of the ground substance become activated. By a series of complex reactions be-

tween a protein component produced by fibroblasts and the mucopolysaccharides, a procollagen, reticulin-like in nature, and finally collagen are formed. Tensile strength increases with the formation of collagen; as the collagen fibers mature, it approaches that of uninjured tissue.

Two periods of wound healing may be considered; (1) the productive or substrate phase lasting from the 1st to 5th day and (2) the collagen phase from the 5th day until healing is complete. During the first phase there is no material gain in tensile strength of the wound. During the second phase collagen is formed and tensile strength gradually increases.

These stages of wound healing have been observed in corneal and limbal wounds. Probably because of the avascularity of these tissues, healing is somewhat slower than that reported in skin wounds.

SUMMARY

Normal corneal wound healing was discussed briefly from gross, histologic, and biochemical viewpoints. Some factors altering normal corneal healing were mentioned.

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Clinical Practice

THERAPEUTICS

STUDIES ON THE OCULAR HYPOTENSIVE EFFECT OF DIAMOX

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The effect of Diamox on intraocular pressure in rabbits was measured in conjunction with measurements of ion concentration, metabolic and blood-fraction changes, and enzyme activity. Intraocular and blood pressures were found to fall by 15 to 20 per cent following intravenous injection of 30 mg. per kg. of Diamox.

Chloride, potassium, and bicarbonate ion concentrations decreased in about 15 minutes, rose to normal, fell again, and gradually returned to normal in 8 hours. Plasma protein, hematocrit, and hemoglobin tests showed the same W-pattern of fall, rise, and fall. Glucose concentration rose, fell, and rose again in an equivalent time period. In metabolic tests, Diamox did not change the O_2 uptake of the ciliary-body epithelium, nor did it appreciably change either the trichloroacetic acid cycle or cytochrome oxidase activity. Carbonic anhydrase activity of the eye was markedly inhibited. Blood pH decreased and specific gravity increased following treatment. In turnover studies, in which Diamox was administered following injection of 1.1 per cent KCl solution to test permeability through the blood-aqueous barrier, potassium ion concentrations increased in blood serum but decreased in aqueous humor by 29 and 11 per cent respectively.

Conclusions are that Diamox lowers ocular tension by inhibiting carbonic anhydrase activity, and consequently causes the concentrations of bicarbonate and other ions to vary. The accompanying changes in aqueous osmotic pressure and the decrease in tissue water that could be demonstrated lowered intraocular tension and slowed aqueous humor production. Diamox does not seem to affect active transport within or permeability of the aqueous humor.

Comment: This paper reviews and confirms the effects of Diamox on the rabbit eye. The authors' findings with respect to tonometry, tonography, fluorescein turnover, and alterations in pH and bicarbonate are in agreement with much of the current literature and compatible with 50 to 60 per cent inhibition of aqueous secretion.

It is difficult to interpret the authors' finding of a fall in aqueous potassium concentration with a rise in serum levels after the intravenous administration of potassium chloride and Diamox. The finding of no measurable effect of Diamox on oxygen uptake by the ciliary epithelium is of considerable interest.

BERNARD BECKER

CORTICOSTEROIDS AND CORNEAL WOUND-HEALING

AN EXPERIMENTAL STUDY

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The anti-inflammatory effect of corticosteroids has been established in ophthalmology as well as in other medical fields. It is also well known that they have no antibacterial action. However, evidence as to their effect on wound-healing is contradictory. Because the anti-inflammatory effects of the corticosteroids is highly desirable in certain surgical situations, a series of studies was undertaken to determine more exactly their effect on wound-healing.

Eighty adult male chinchilla rabbits were treated with standard incisions 2 mm. within the limbus, and the eyes were treated with heparin to prevent excessive fibrinization. The animals were then divided into five groups, one for control and the others for experimentation.

Twenty rabbit eyes were treated twice daily with an antibiotic ointment, and tensile strength of two eyes in two rabbits recorded daily. Fourteen eyes were treated twice daily with antibiotic ointment, and once daily cortisone, 3 mg. per kg., was injected intramuscularly, and tensile strength recorded daily. Eighteen eyes were treated twice daily with topical metasteroid ointments, and tensile strength tests carried out daily. Fourteen eyes were treated twice daily with topical metasteroid ointment and cortisone, 3 mg. per kg., was injected intramuscularly daily. Six eyes were treated with antibiotic ointment daily, and systemic cortisone, 3 mg. per kg., was given beginning on the 3rd day after operation. Pressure studies were similar after all treatments, and observation extended over 10 days in each experiment.

When only the antibiotic ointment was used, pressure resistance increased greatly for the first 3 days. Intramuscular cortisone in doses comparable to those used for human beings began to retard wound healing after 48 to 72 hours. Topical steroid ointment retarded wound-healing much more than systemic injection of corticosteroids, especially during the first 4 days. The combination of topical and systemic administration of corticosteroids had the same effect as the local ointment for the first 3 days, but after that retardation of wound

healing was accelerated. Systemically administered cortisone, however, has no effect if it is started after the 3rd day.

The different effects of topical and systemically given corticosteroids may account for discrepancies between the observations of other workers, some of whom used topical ointments and other systemic injection.

Comment: Apparently the last word on steroid influence on corneal wound healing has not been written. This latest study by Lieb and his associates would indicate that steroids do have an influence on wound healing as has been demonstrated by most earlier observers not only histologically but also under various testing conditions. The method employed by Lieb and his associates indicates that steroids have an influence during the first 3 days, particularly when they are locally applied. Early in the studies of steroids it was indicated by many investigators that steroids do have an influence on the initial laying down of tissue repair elements but had no influence on these elements once they had formed. The Lieb studies would confirm this initial impression. The difference between the influence of local and systemic administration could be due to the concentration of the steroids present at the local tissue level, a greater concentration being obtained by local administration perhaps than by the systemic route. Particularly this is a likely possibility if the wound were central. It is not a likely explanation for differences in effect on limbal wounds. It would suggest also that steroids not be used until 2 or 3 days after surgery but, if they must be employed to control inflammatory processes which might be hazardous to the eye during the recuperative phase, the systemic route would be superior to the local route during the early stages of repair.

IRVING H. LEOPOLD

EFFECT OF THE XANTHOPTERIN ON THE EXPERIMENTAL WOUNDS OF THE CORNEA

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It has been shown that xanthopterin accelerates the growth of cultures *in vitro* of cells derived from different organs. At the same time it was also shown that xanthopterin impedes in a high degree the proliferation *in vitro* of neoplastic cells.

The action of xanthopterin in the acceleration of the growth of cultures *in vitro* of normal cells deriving from different organs is the subject of the present study. It was of particular interest to study the effect *in vivo* of xanthopterin on the regeneration of the cellular elements of the cornea that had been wounded experimentally. The cornea, due to its anatomical peculiarity (presence of tis-

TABLE 1

Experiment	Time of Cicatrization in Hours of Round Abrasion of Corneal Epithelium 8 mm. in Diameter	
	O. S. (control)	O. D. (treated)
1	120	96
2	120	96
3	120	102
4	110	96
5	115	96
6	120	104

sues of epithelial and mesenchymal origin) and especially due to the absence of vessels, presents many analogies with tissue cultures *in vitro*.

Research was carried out on rabbits. The first part of the experiment consisted in limiting in both eyes a circular zone of the cornea by means of a small borer 8 mm. in diameter; this zone of the cornea can be rubbed off from the epithelium with a small knife. The operation was carried out together with coloring of the cornea by fluorescein. In another series a wound in the whole depth of the center of the cornea was made with a lancet in both eyes.

The histologic examination of the sections of the wounds in all depths showed an increase in the process of cicatrization of the corneal tissue under the action of xanthopterin.

Comment: On a number of occasions it has been reported in the literature that substances will accelerate corneal wound healing. Various amino acids, whole blood, and chlorophyl are examples. These observations have not always been confirmed in subsequent studies. The apparent property of xanthopterin when employed in an ointment vehicle in 0.1 per cent concentration warrants further study as it could have some practical value and be useful in understanding factors that control wound healing.

IRVING H. LEOPOLD

EIN NEUES VERFAHREN ZUR BEHANDLUNG DER KERATITIS HERPETICA

A NEW PROCEDURE IN THE TREATMENT OF KERATITIS HERPETICA

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Because the transplant eventually becomes cloudy, the operation for keratitis herpetica is usually reserved for cases that do not respond to conservative treatment and for whom no improvement of sight can be expected.

With the idea that the curative effect of the transplantation might be attributable to the trepanation alone, that is, section of the corneal nerves, the author devised the simple operation of "incisio corneae." The first subject was a 66-year-old man who had been treated for 2 months for severe herpetic keratis. After cocaine anesthesia of the eye, a circular incision up to the Descemet membrane was made with a 7-mm. trepan. After instillation of scopolamine and an antibiotic, the eye was bandaged. Photophobia, tearing and pain disappeared the next day. The patient was able to leave the hospital in 8 days with 0.2 vision. Six months later the vision was 0.6.

The author has used this procedure on 12 patients, 7 of whom have had no recurrence for at least 6 months; for the other 5 the interval from the operation to the time of writing was less than 6 months. All 12 were able to leave the hospital within 6 to 8 days with good vision. At first only patients who did not respond to conservative treatment were subjected to the operation. Later the operation was done at the start of treatment.

The advantages of the procedure are: (1) it is short, simple and safe; (2) no special instruments or knowledge are required; (3) it can be used with equally good results in beginning light cases and in more severe cases of longer duration; (4) the duration of postoperative treatment is reduced from 6 to 8 weeks to about a week; (5) the clearing of the cornea and improvement of sight is more pronounced in the severe cases; (6) no damage can be done to early cases with good visual faculty; and (7) from the therapeutic viewpoint it is equal to curative keratoplasty, and from the optic standpoint superior to it.

Although the number of cases is small, the good results obtained in all of them seem to warrant further trials with the operation on a larger number of cases.

Comment: This operative treatment of herpetic keratitis is of interest in view of the success now being attained with lamellar grafts. The author claims immediate cessation of subjective symptoms and rapid healing of the keratitis—results which he believes to be due to section of the corneal nerves. The article does not seem to be documented sufficiently to warrant the conclusions drawn, but the method is certainly worth testing, particularly in herpetic keratitis of rabbits.

PHILIPS THYGESON

RESULTS OF ROENTGENOTHERAPY WITH HARD RAYS IN THE TREATMENT OF IRIDOCYCLITIS

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Ophthalmologica, 1959, *138:* 138–145

From 1950 to 1957, that is to say, during 8 years, 958 patients with iridocyclitis of various etiology were treated radiologically with hard rays. The results obtained by this method were:

Cured.....62 %
Improved.....27 %
Stationary....10 %
Worse..... 1 %

The deteriorations were in no case due to the roentgenotherapy. The duration of the illness was abbreviated and the irradiation caused neither direct nor later damage. There was follow-up during several years, and no incidence of cataract occurred. This method has been used in the Coltea Hospital of Bucharest since 1950.

It has become possible to avoid the dreaded complication of cataract in roentgenotherapy of inflammatory ocular affections by the use of a tension of 180 to 200 kv. and a heavy filter. The authors use constant elements of technique for this treatment which are applied in all forms and stages of iridocyclitis. For more individualized treatment they also use a series of variable elements, adapted to the requirements of specific cases. The constant elements of the technique are 180 to 200 kv., 0.5 mm. Cu, 40 cm. distance; the variables are concerned with the dosage at each treatment, the rhythm of irradiation and the total dosage. In acute cases, the dosage at each treatment is from 30 to 60 r, and repeated, according to the reaction observed, after 24 to 48 hours. Irradiation of such forms is continued until the inflammatory process is terminated. If there is a tendency to slight remission, the treatment is continued until 500 to 700 r, and even more, administered in small fractions.

In the case of chronic inflammations, a quantity of 300 to 400 r, administered in doses of 60 r every other day, is usually adequate; then an intermission of 3 to 4 weeks is observed. In these chronic cases we must not take an immediate success for granted: the tendency to involution and resorption of the lesions continues for 3 to 4 weeks after the end of the treatment. No other therapeutic methods should be resorted to during that period except in the case of an aggravation of symptoms. If the condition remains stationary, the treatment can and should be repeated after 4 weeks.

It may be summarized that roentgenotherapy is indicated in iridocyclitis of various etiologies: rheumatic, tuberculous, allergic, traumatic, postoperative, since it facilitates the action of the natural defense mechanism of the organism. To some extent success depends upon early application of roentgenotherapy.

Comment: This form of therapy is not very popular in the treatment of uveitis in this country. The chief drawback has been the possibility of inflicting further trauma on an eye that is already diseased. Included in this is the threat of early or late cataract formation. The results are very impressive and the freedom from complications are encouraging. It certainly represents another of the nonspecific therapeutic approaches to this ocular problem and bears further investigation but only in the hands of a capable radiologist.

IRVING H. LEOPOLD

ANAPHYLACTIC SHOCK AFTER THERAPY WITH PENICILLINASE

A. L. HYMAN

New Orleans

J.A.M.A., 1959, *169:* 593–594

Penicillinase, first reported in 1940 by Abraham and Chain, has been used chiefly to inhibit penicillin activity in culture mediums. In 1956 Becker reported its use for the destruction of penicillin in both guinea pigs and human beings. Since then it has been increasingly used to treat penicillin reactions. Untoward reactions following intramuscular injection in the gluteal area have been few and mild, consisting of morbilliform rash, and a brief period of generalized weakness and malaise. Similar reactions have been more frequent after intravenous injection.

A 50-year-old woman, previously well, developed dyspnea and pleuritic-type pain on the right side, for which she was hospitalized in another area without finding a cause. Two months later she came under our care for the same complaints, with the addition of sore throat and a cough which was productive of yellow sputum. After careful examination, she was given 600,000 units of procaine penicillin intramuscularly and advised to stay in bed. Six hours later increasing symptoms of penicillin reaction appeared, and, since the patient recalled a similar experience following use of penicillin several months earlier, 800,000 units of penicillinase were given in 2 cc. of sterile water into the gluteal muscles by injection. Within 2 minutes she complained of weakness, dizziness, and dim vision, and within a short time orthopnea, wheezing respiration, and cyanosis appeared. She improved after intravenous injection of epinephrine, and was placed in the hospital where she recovered on intensive treatment with epinephrine, steroids, and careful nursing.

Penicillinase is a protein enzyme secreted by *Bacillus cereus*, *Escherichia coli*, and many strains of staphylococci. It hydrolyzes penicillin to the antigenically inert penicilloic acid, but is not itself destroyed or changed by the process. The fact that it is a foreign protein may explain allergic phenomena, especially after repeated exposure. Antibody formation has been reported in experimental animals.

(*See editorial comment following next article.*)

PENICILLINASE THERAPY

Clinical Report of Severe Reactions

Milton Reich

New York

J.A.M.A., 1959, *169:* 594–595

Penicillinase is an enzyme which destroys penicillin both *in vitro* and *in vivo*, and is thought to act by hydrolyzing penicillin to penicilloic acid, which is not antigenic. It has been reported to be effective in the treatment of penicillin reactions, but local and febrile effects have been observed following its use. Fisher has induced antibody formation in experimental animals by repeated injections. Since penicillinase is a protein, repeated exposure might lead to a significant number of antibodies in human beings, and nonspecific reactions to protein might also occur.

Two cases are reported. The first patient was given intramuscular injections of penicillin for 3 days as treatment of respiratory infection, and 8 days later developed hives, itching, and arthralgia of the hands, ankles, and knees. Intramuscular injection of 800,000 units of penicillinase led to shaking chill, slight respiratory difficulty, cyanosis, and rise in temperature to 103° F. The patient responded well to adrenocorticotropin and prednisone. Persisting urticaria vanished after a second injection of penicillinase, which was followed by swelling of the buttocks.

The second patient was given penicillin after a motorcycle accident, and 10 to 12 days later developed severe hives which did not respond to antihistamines. He was hospitalized and the hives controlled with steroid therapy, but they returned as soon as the treatment was discontinued. Intramuscular injection of 800,000 units of penicillinase into the deltoid region was followed by local swelling, erythema and pain, and shortly also by lethargy, nausea, chill, and fever, and the patient finally became comatose. Ten days later a second dose of penicillinase for the urticaria resulted in a similar reaction, after which he slept for 30 hours. A month later he still had angioneurotic edema of the face.

Comment: Penicillinase can be helpful in inactivating penicillin and thus reduce the reactions to it. It is important that ophthalmologists be aware of the complications and the reactions of penicillinase as well as its potential beneficial effect.

IRVING H. LEOPOLD

OPHTHALMIC USE OF NOVOBIOCIN

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Columbus, Ohio

J.A.M.A., 1959, *169:* 580–582

Novobiocin is a new antibiotic derived from cultures of *Streptomyces niveus* or spheroides. It is highly effective against most Gram-positive organisms, but only variably so against Gram-negative bacteria. It has been recommended for use either alone or with other antibiotics for eye infections.

In the present study, the effect *in vitro* of novobiocin was studied on 270 strains of bacteria from 264 patients with eye infections. Studies *in vivo* were also carried out in 30 patients with various types of external eye infection, with a 1 per cent concentration in ointment every 3 hours during the day. Eye cultures were made before treatment, and effects were evaluated 3 to 5 days later.

All 225 strains of staphylococci (both coagulase-negative and coagulase-positive) isolated from the eyes were sensitive to novobiocin *in vitro*, as were 5 strains of diplococcus pneumoniae, 15 strains of α- and β-hemolytic streptococci, and 13 strains of *Pseudomonas aeruginosa*. On the clinical test, the drug cured eye infection in all but two cases, in one of which the organism was Candida and in the other was probably a virus.

The most important factor indicating use of an antibiotic is the severity of the infection. A major infection which threatens life, sight, or appearance, warrants immediate and vigorous antibiotic therapy while laboratory studies are in progress. The Gram stain should be done at once as a guide in selecting the correct antibiotic. Novobiocin is almost certain to be effective in Gram-positive infections and should be used both topically and systemically. On the other hand, common, superficial eye infections can usually be managed with carefully selected antibacterial drugs and do not therefore warrant culture and sensitivity studies, or routine use of novobiocin.

In selecting an antibiotic, the known percentage of resistant bacterial strains and the incidence of different strains in eye infections is also considered. Suie has tabulated strains of staphylococci isolated from 115 patients with conjunctivitis, indicating their susceptibility to 11 antibiotics. Since these organisms develop resistance to novobiocin as well as to other antibiotics, systemically usable antibiotics should not be promiscuously used for common and insignifi-

cant infections. Topical drugs delay development of resistant organisms and are usually more effective against these infections than the systemically active drugs.

Novobiocin is well tolerated in doses of 0.5 gm. every 6 hours. Minor side reactions are fairly frequent, but it is comparatively nontoxic otherwise. Penicillin or tetracycline combinations with novobiocin are said to have synergistic effects and to delay development of resistant strains. Novobiocin is applied to the conjunctiva in concentrations of 2.5 per cent or over. More than 1 to 2 mg. are not well tolerated as an intraocular injection. The drug does not penetrate injured eyes well, but effective intraocular levels are obtainable in cases of corneal epithelial loss and of damage to the blood-aqueous barrier.

Since improperly diagnosed and treated eyes are sometimes seen, the need for accurate differential diagnosis should be emphasized.

Comment: Novobiocin is a useful antibiotic against Gram-positive organisms. The reviewer is in complete agreement with Dr. Suie and his co-workers in stressing that the use of this effective agent should be limited to those intraocular infections which appear to be due to Gram-positive organisms that are not responsive to more commonly employed antibiotics. It is an antibiotic which should be kept in reserve and not used routinely. In this way, we will have another effective agent to which organisms have not had a chance to become resistant.

IRVING H. LEOPOLD

SURGERY

A SIMPLIFICATION OF BLASCOVIC'S PTOSIS OPERATION

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Zabrze, Poland

Polish Medical History and Science, 1959, *2:* 24

Blascovic's procedure is widely considered one of the best operations for ptosis, but it requires considerable time. The author has therefore developed a simplification consisting essentially in excising the conjunctiva parallel to the border of the tarsus, which is then shortened and freed with the levator to be used together as a flap. M. and S. Vannas of Helsinki use a similar simplification, but do not dissect the conjunctiva at the beginning of the operation; they separate it later from the levator by blunt dissection, a procedure which may be difficult if the levator is thin or the conjunctiva or adjacent tissue scarred.

The author's procedure is as follows: (1) under local anesthesia the conjunctiva is incised parallel to the tarsus and close to its border, carrying the incision

the full length of the everted lid. Three double-armed silk sutures are placed through the edge of the conjunctiva. (2) A section of tarsus 2 to 3 mm. wide is dissected, and the tarsus and levator are freed together from the fascia and mobilized to form a flap. (3) A muscle clamp with 24 mm. blades, modified from Blascovic's original clamp, is placed on the tarso-muscular flap just below the level at which the shortening is to be done. (4) The sutures placed through the conjunctiva in step *1* are then passed through the levator about 2 mm. above the muscle clamp. (5) The levator is cut just above the clamp. (6) A second set of three double-armed silk mattress sutures are placed between the surface of the muscle and the lid, forming the orbito-palpebral fold. (7) The three first sutures (used in steps *1* and *4*) are then drawn through the skin of the upper lid between 2 and 3 mm. above the edge.

The conjunctiva and the shortened levator are thus brought to the cut surface of the tarsus, advancing the levator and re-forming the cul-de-sac. All sutures, as in the Blascovic method, are tied through small glass beads, and the free ends are fastened to the cheek with adhesive to hold the lids closed. The next day, when the upper lid is swollen, the sutures are cut, and are removed in 7 to 10 days.

Comment: As in every other branch of surgery, ophthalmologists are always trying to devise methods to shorten the duration of the procedure. Despite the fact that there are now approximately 100 methods described for correcting ptosis, there basically remain 3 general procedures to follow; *i.e.*, attach the levator to the superior rectus, suspend the lid from the brow and, lastly, shorten the levator muscle. As a primary procedure most surgeons prefer to attempt to shorten the levator muscle. Despite the fact that the anatomical dissection of the tissues is usually very satisfactory, the end result is frequently disappointing to both the surgeon and the patient. The main advantage of the procedure described would appear to be that by resecting part of the tarsal plate one would not miss any of the levator fibers since they are attached both along the anterior surface of the tarsal plate and the upper edge of the tarsal plate. There are some surgeons, however, that would prefer not sacrificing as much of the tarsus as recommended by the author. Though the operation would appear to be easy to perform, the results would probably be no better than with the other procedures which have already been described.

P. Robb McDonald

EXTRAOCULAR MUSCLES

NONSURGICAL TREATMENT OF CONVERGENT STRABISMUS

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California Med., 1959, *90:* 429–432

In discussing the nonsurgical treatment of convergent strabismus, the author stresses two relatively recent trends: (1) the use of miotics, and (2) pleoptics. He also believes the use of the term strabismus in referring to manifest deviations should be discouraged. From a practical standpoint, esotropia is much more succinct than convergent strabismus and certainly easier to say.

The treatment of esotropia, whether surgical or nonsurgical, should be directed toward some specific goal, and this goal, at least at present, is so-called "functional cure." According to Costenbader (1958), the end result should include the best possible vision in each eye, the best possible binocular alignment with harmonious movements, and the most secure single binocular vision possible. This therapeutic ideal is attained in only some 10 per cent of patients even under optimal conditions. Some ophthalmologists maintain that a small-angle esotropia with good cosmesis and freedom from heterophoric asthenopia is a more than adequate substitute, but it would seem that this falls short of the delicate interocular balance intended by nature.

The nonsurgical treatment of esotropia can be logically subdivided into four distinct, though interrelated, categories. (1) The psychiatric approach is based on the frequent relationship between changes in the degree of tropia and variations in the emotional status of a given individual. Perhaps this should be called psychologic rather than psychiatric, in view of the more sordid implications of the latter. (2) The mechanical approach involves the prescription of optical devices worn by the patient to change the direction or the intensity of light rays entering the eye—occlusive devices, spherical and cylindrical lenses and prisms, for example. (3) In the sensory category, emphasis is placed on the more central as opposed to the peripheral aspects of tropia. Until recently, sensory treatment—"orthoptics"—has been directed toward binocular function; little attention has been paid to improvement of visual acuity in the deviating eye, except for total or partial occlusion of the unaffected eye. In "pleoptics," primary attention is given to visual improvement in an amblyopic eye, but secondary benefits regarding both position and binocularity also accrue. (4) The pharmacologic treatment is essentially a mechanical approach to the problem of esotropia, except that the structure or function of the eye is altered by the use of drugs rather than by the changes in light-wave pattern that are brought about by lenses of various types.

With reference to the psychologic treatment, it may be said that most ophthalmologists are aware of the effect of emotional unrest on the relative positions of the visual axes. Too often, however, this effect is disregarded in an attempt to reduce the problem to its simplest form and thereby better the chances of a permanent cure. Campion (1958) stated that such oversimplification may act adversely in certain patients inasmuch as surgical treatment as such may have a great deal of psychotherapeutic value, so that the danger of overcorrection is great. Conservatism is to be advocated in the presence of a large functional factor.

The mechanical treatment of esotropia is directed toward the achievement of the best possible visual acuity in each eye and the best possible alignment of the visual axes. Total or partial occlusion of the better, or fixating, eye is employed in an effort to improve vision in the deviating eye. Since fusional requirements are best met when the retina receives the clearest possible image, full correction of astigmia and myopia should be ordered at the outset. In the case of myopia, no harm and often some benefit will accrue from the elimination of minus power for close work. In hyperopia, in which visual clarity may exist throughout wide ranges of refractive error, correction is directed, not to acuity, but to the elimination of the accommodative component of the "near reflex." Full hyperopic correction provides maximal visual acuity with minimal accommodative stimulus. The less the accommodative effort, the less the associated convergence; and the less the convergence, the less the tendency toward esotropia. This does not mean, however, that all cases of esotropia are due to uncorrected hyperopia, or conversely that esotropia cannot be present in the absence of hyperopia.

In the sensory treatment of esotropia, orthoptic exercise, as now known, consists of active binocular stimulation of corresponding retinal elements. The first step is to eliminate anomalous retinal correspondence, which is quite difficult if the angle of anomaly is small. Next, an attempt is made to overcome suppression of image, the purpose being to re-establish the patient's awareness of any abnormal deviation between the visual axes. Finally, attention is given to improvement of fusional amplitudes so that comfortable binocular vision that records a single image can be maintained in the face of rather wide fluctuations in relative visual direction. The proper use of orthoptic treatment obviously depends on a rather exact knowledge of just when corresponding retinal points are being stimulated. Further, since the fovea is commonly used as a reference point, it follows that the therapist must ascertain whether there is true foveal fixation or eccentric fixation.

"Pleoptic" treatment attempts to overcome the hurdles of amblyopia and eccentric fixation. The premises of this treatment are (1) equal acuity in both eyes is paramount in the establishment of single binocular vision; (2) defective vision in the deviating eye is most commonly the result of eccentric fixation; (3) occlusion of the fixating eye reinforces eccentric fixation in the other; hence visual acuity fails to improve and further therapy is more difficult; and (4) eccentric fixation can be converted to foveal fixation through adequate training.

This is based, first, on foveal recognition and, second, on visual-manual coordination.

The first premise is not subject to serious challenge. As to the relationship between defective vision and eccentric fixation, two cases reported by Mayweg and Massie (1958) are of interest. In both, esotropia was observed during the first few months of life and the ordinary occlusive techniques were used with no success. At age 5, both patients had vision poorer than 20/200 in the deviating eye, and both had eccentric fixation. After pleoptic treatment both patients had 20/20 vision and foveal fixation.

The armamentarium of pleoptics consists of instruments designed to (1) diagnose eccentric fixation, (2) temporarily blind the parafoveal area, and (3) stimulate the fovea. In addition, there are devices designed to coordinate the eye, the cortex, and the hands. The term *pleoptics* was coined in 1940 by Bangerter in reference to his series of exercises directed toward such coordination. Unfortunately, Bangerter's equipment is cumbersome and expensive. Primarily for this reason, the spreading interest in pleoptics has centered around the instruments devised by Cueppers. These are the visuscope, the euthyscope, and the coordinator, three relatively small and inexpensive devices.

The results ascribed to pleoptic training appear quite impressive. Thus, in a series of 50 cases reported by Mayweg and Massie (1958), improvement to 20/20 vision occurred in almost 80 per cent. Before treatment, vision ranged from 20/60 to less than 20/400, and in all but 8 cases occlusion of the affected eye had been carried out without any measurable improvement in visual acuity.

In the pharmacologic treatment of esotropia, both cycloplegic drugs (atropine, for example) and miotics (isofluorphate, pilocarpine) have been advocated, however paradoxical it may seem that drugs so opposite in action could both accomplish the same result, namely, reduction in the degree of deviation. Contrary to Guibor's opinion (1958) that atropine reduces hypertonicity of accommodation and therefore hypertonicity of associated accommodative convergence, the general belief is that, although atropine does in fact reduce accommodation by paralyzing the ciliary muscles, it does not alter accommodative effort, but may even stimulate it as the patient attempts to overcome the cycloplegic effect. Assuming that accommodative convergence is directly related to accommodative effort, the degree of esotropia might be expected to increase rather than decrease. This it does, in many cases. The use of atropine is probably best reserved for cases in which occlusion is desired but cannot be maintained by mechanical means; particularly in high degrees of hyperopia, atropine affords quite effective physiologic occlusion.

The value of miotics in the treatment of esotropia was recognized by Javal as early as 1896. The more recent stimulus toward their use has come largely from Abraham. In reporting on the benefits obtained by the use of pilocarpine in patients with concomitant esotropia, he has emphasized the fact that treatment should be continued until the age of 8, at which time the fusion faculty has matured. Permanent cure can frequently be achieved after divergence amplitudes

have sufficiently improved. Isofluorophate (Floropryl) is now the drug of choice, rather than pilocarpine, because its effect lasts longer.

The most obvious explanation of the beneficial effect of miotics lies in the fact that they produce peripheral accommodation without central accommodative effort and associated convergence. They thus reduce the degree of hyperopia and shorten the distance to the *punctum proximum*, which makes them particularly valuable in the treatment of the so-called "hypo-accommodative" esotropes. Another explanation, and one that has received no attention in the literature, has to do with pupillary contraction rather than ciliary spasm. If the drug reduces the pupil to 1 mm., the effect is that of a camera with a focal length of about 25 mm. and an aperture setting of *f*25. Such a camera would give satisfactory resolution of objects at distances between infinity and about 20 inches from the lens. Thus a large part of the benefit of miotics probably accrues not only from decreased hyperopia but also from a decreased need for accommodation to maintain a sharp image on the retina.

Comment: The advice to be cautious before operating on cases of esotropia in which there is a "large functional factor" is sound since there is a great danger of producing an overcorrection. These cases are a real problem as they frequently do not respond to conventional nonsurgical therapy. Moreover, our experience in treating them with sedatives such as phenobarbital or tranquillizers such as meprobamate has been totally ineffectual. If the deviation is grossly apparent, one must resort to surgery. Our practice is to aim to correct the minimal measured deviation and hope for the best.

I have little to comment on his subdivision of mechanical and sensory treatment except to reiterate the opinion that the place of pleoptic treatment awaits further definition. Certainly, the great majority of our cases with amblyopia respond to occlusion of the nonamblyopic eye. The few who fail to respond to adequate occlusion should warrant a trial of pleoptics. The value of this method of treatment can then be judged by the number of these cases in which the visual acuity can be normalized. Certainly the instigation of pleoptic therapy for every case of amblyopia is a most luxurious form of treatment.

Finally under miotic therapy it has been our experience that the size of the pupil has little to do with the effectiveness of this form of therapy. Moreover, the mode of action of the miotic, isoflurophate, now seems to be a facilitation of accommodation rather than the inducing of peripheral accommodation for it frequently can be used in patients without hyperopia or with mild myopia without decreasing visual acuity. This has been substantiated experimentally by Jampolsky in a paper due for publication in the near future.

PHILIP KNAPP

EXTERNAL DISEASE

EYE COMPLICATIONS OF VARICELLA

M. G. Bonamour and Mlle. Gaillot

J. méd. Lyon, 1959, *No. 950:* 663–669

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Both ophthalmologists and pediatricians know well that eye complications may follow various eruptive diseases of childhood. The viruses which attack the skin may also attack the ocular structures of epithelial origin, and meningoencephalic complications may affect the nervous organs of the eye. Ocular complications of varicella are perhaps the least well known, because of their comparative rarity in relation to the extreme frequency of the disease, its mildness, and the prevalence of subclinical cases. Finally, complications often do not appear until some time after the attack is over so that the connection is not considered.

The virus has been studied for some time, and there is considerable evidence that it is identical with the virus of herpes zoster, the latter representing reactivation of the varicella virus in partially immunized persons.

Conjunctival symptoms, consisting of inflammatory reactions or eruptions, may precede the skin eruptions. Both conjunctiva and lids may be involved during the period coinciding with skin eruption. The lids may present the development of papule to vesicle which is typical of the skin lesions, and these eruptions are subject to the same complications as the skin eruptions.

Corneal lesions are of two main kinds. The first takes the form of ulcerative keratitis. Marginal ulcers may follow small vesicles on about the 6th day, but leave no visual handicap. Central ulcers, which appear on about the 10th day, may leave scars which interfere with vision, or they may cause functional amblyopia in small children. The second type of corneal lesions is a disciform or neuroparalytic keratitis appearing a month or two after the varicella has disappeared. It may take several forms varying somewhat in site, extent, vascularity, or neuropathic character.

Uveitis is a rare complication in children, is usually mild, and regresses leaving no sequellae.

Varicella encephalitis may involve the optic nerve, the pupillary nerves, or the oculomotor nerves, but such involvements are very infrequent. Acute disseminated perivenous encephalitis may cause varied systemic symptoms, usually mild. In some instances it involves only the eye nerves, but usually other nervous symptoms are also present. Affection of the optic nerve may resemble retrobulbar neuritis or edematous papilitis. Complete optic nerve atrophy has been reported, but usually the patient recovers completely within a few months. Ordinarily oculomotor trouble regresses rapidly regardless of severity. Paralysis of intrinsic muscles may involve the pupil.

Six cases of congenital eye complications following maternal varicella during gestation have been reported. These include optic atrophy, retinal pigmentation, and crystalline lesions like those observed after maternal rubella.

In view of the frequency, mildness, or subclinical nature of varicella, it is possible that a number of children's eye syndromes can be attributed to varicella even when the actual context cannot be proved.

Comment: The ocular complications of chicken pox are uncommon and diversified. A general review such as the one by Bonamour and Gaillot is worth while for it summarizes the observations on the subject and assembles the few reports that are scattered in the literature.

Recognition of the eye complications during the eruptive phase of varicella usually offers no diagnostic problem. On the other hand, the clinician or the patient may not associate an acute attack of keratitis, uveitis or neuroophthalmologic disturbance with the uncomplicated case of chicken pox that the patient had weeks ago.

There is no specific therapy for chicken pox. γ-Globulin and hyperimmune serum have been only partially, if at all, successful in preventing and treating the disease. Fortunately the prognosis is good, even without therapy, when complications appear.

The effects of steroids in varicella are interesting and important. They are similar to those noted by Apt and Leopold in an analysis of the reported cases of herpes zoster ophthalmicus treated with steroids and ACTH (to be published in Surv. Ophth., *5*, Dec., 1960). This is not too surprising since epidemiologic and experimental evidence points to the fact that the two diseases are due to the same virus.

The timing of the steroid treatment is extremely important in determining the effect produced. Cortisone and related derivatives have been observed to have a beneficial effect in complications of varicella such as pneumonia. Strachmann (J. Pediat., *46:* 327, 1955) described a case of uveitis that appeared during the convalescent stage of chicken pox which promptly subsided when cortisone was given. The steroids probably have little effect on previously acquired immunologic resistance (antibodies have already been stimulated by the time the varicella rash has appeared) and they do inhibit the local inflammatory response. In contrast, a severe fulminating form of the disease has occurred in patients who have contracted chicken pox while getting steroid therapy. In this situation the immune mechanism has not been started and it is probably modified in association with the inhibition of inflammation.

The timing of steroid therapy related to the effect produced, however, is not absolute or as clear-cut as outlined above. Moreover, recall the report of Shee (Brit. M. J., *2:* 82, 1953) who observed the reactivation of the chicken pox virus in a child by cortisone therapy that was used for penicillin hypersensitivity.

Since the experience with steroid therapy of the ocular complications of varicella is so meager, we must use these drugs with utmost caution. We know only too well the deleterious effect of cortisone on one other relatively innocuous and prevalent virus—herpes simplex—when it attacks the eye.

LEONARD APT

TUMOURS AND CYSTS OF THE LACRIMAL CARUNCLE

ROWLAND P. WILSON

Dunedin, New Zealand

New Zealand M. J., 1959, *11(Suppl.)*: 23–32

Tumours of the lacrimal caruncle are rarely reported, the most important study in English being the analysis of 200 cases collected by Evans by means of a questionnaire. The author reports 107 cases which he either saw clinically or knew by study of biopsy material during 19 years in Egypt.

The lacrimal caruncle contains both ectodermal and mesodermal structures, but is essentially a skin structure and therefore pathologic lesions in the caruncle are similar to those in the skin, more particularly in the eyelid. While the incidence cannot be determined, the condition is certainly very rare, even though the small size of the lesions probably means that they are often overlooked. Apparently tumors of the caruncle may occur at any age, but in our series no malignant ones were seen below the age of 45. Injury has been mentioned as a possible causative factor, but the exposed position and our experience in Egypt suggest that irritation and infection are more important.

While the exact percentages vary somewhat, both Evans and Serra found that papillomas were the most frequent lesions. Evans placed melantic tumors second and Serra reported epitheliomas as second in frequency. In Evans' series, 19 per cent were malignant. Our Egyptian series included very few papillomas, but a large proportion of granulomas and retention cysts, with 17 per cent melanomas.

The first sign is usually a slight enlargement or change in color. Most commonly tumors consist of smooth, rounded, reddish papillomatous forms; or pinkish, translucent, elevations, occasionally with vessels on the surface. Solid tumors may be nodular, with pinpoint whitish or yellowing areas. Benign tumors are confined to the caruncle, but malignant ones often encroach on the plica semilunaris. There are rarely other symptoms, though the patient may complain of a feeling that there is something in the corner of his eye, or occasionally of pain. Large lesions may lead to epiphora. Malignant tumors are indistinguishable from benign except that they tend to be flatter and more nodular and to spread into other structures. The surface may ulcerate, and chemosis may appear in the conjunctiva. Malignant tumors are also less mobile, and as they become invasive they tend to bleed.

Excision of benign tumors or of malignant ones which are confined to the caruncle present no special problems, but all new growths in the caruncle should be widely excised as a routine precaution. Because postoperative irradiation is so effective in controlling epitheliomas, radical operation may not be necessary in these cases, but is usually essential in cases of melanoma. There is some difference of opinion as to whether all small pigmented areas should be removed.

Comment: Tumors of the caruncle in ordinary practice are quite a rare ophthalmic lesion. The majority of them are of importance chiefly from cosmetic appearance. The

commonest lesions in our experience are the retention cysts and the pigmented nevi. The percentage of malignancy quoted, both in the literature and from the author's series, seems to be quite high when compared with the experience of most pathology laboratories in this country.

Surgical removal is rather simple and presents no particular complications. Therefore, in the majority of these cases, surgical removal is indicated even in the absence of potential malignancy. Inasmuch as the pigmented lesions are usually quite obvious in this group, extirpation is particularly indicated.

T. E. SANDERS

DOES A RELATION EXIST BETWEEN EARLY OCCURRENCE OF ARCUS LIPOIDES CORNEAE AND CORONARY ATHEROSCLEROSIS, ESPECIALLY CARDIAC INFARCTION?

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Ophthalmologica, 1959, *138:* 118–133

Arcus lipoides corneae is a condition marked by crescentic deposits in the cornea containing fat and cholesterol crystals. The width of the crescent rarely exceeds 1 mm. In rare cases a double arc occurs. According to the literature arcus lipoides usually occurs first at the upper circumference of the cornea, as approximately one third of a circle. A corresponding arc at the lower circumference follows; the two arcs may coalesce. This is found more frequently on the nasal side than on the temporal one.

The author's observations differed as to the site of arcus lipoides. Arcus lipoides was more frequently found to be more developed at the lower circumference; sometimes, even with focal lighting, it was only visible at the lower circumference. This observation supports the author's opinion that outside local factors significantly influence the formation of arcus lipoides.

Many authors have discussed the problem of possible general medically diagnostic significance, that is clinical value, of arcus lipoides. The present investigation was based on an examination of 48 patients with arcus lipoides and 16 patients after cardiac infarction. While conclusions as to the possible relation of these two pathologic entities may be reached on such a basis, the number of patients is not adequate for statistical data. Comparative clinical and laboratory observations were made. The carriers of arcus lipoides were in the age group under 56 years. The basis for the group of 16 patients after cardiac infarct, of the same age group, were more than 2,500 patients who had been examined electrocardiographically at the Medical Clinic in part of 1957.

A comparison of clinical findings in the two groups showed that in the patients with arcus lipoides no significant increase of objectively ascertained arterio-

sclerotic disease, especially of the coronaries, could be found. Neither could an increase of the incidence of arcus lipoides be ascertained in the patients after cardiac infarction by means of the methods of investigation employed in this study. If only the more severe cases of arcus lipoides, those in which the disease could be readily recognized in daylight, were considered, the absence of increased incidence was even more pronounced. A close correlation between the two syndromes could, then, not be established on the strength of the present studies. For statistical purposes a much larger number of cases with arcus lipoides in this age group would be necessary since cardiac infarct is comparatively rare at that age. On the other hand it was found in all patients with arcus lipoides, from both groups, that local factors (inflammation, and particularly outside physical and chemical influences upon the eye) may be markedly influential in the formation of arcus lipoides. This holds especially true in genetically predisposed persons.

The laboratory investigations showed up the basic differences between these two groups of patients, so that they did not provide a basis for a correlation between them either. The frequent occurrence of high ester fractions was striking; in patients after cardiac infarction it seems often to be above 0.8. This can only be presented as an observation, since a significance for the present studies could not be established with certainty.

Comment: Since the author of the article "Bestehen Beziehungen zwischen dem fruhzeitigen Auftreten eines Arcus lipoides corneae und Zirkulationsstorungen des Herzens, insebesondere dem Herzinfarkt?" in conclusion of his studies reaches only a negative result it seems to me that it is really not of general interest although it might be a good building block for somebody specially working on such problems. The study comes from a very good clinic and the abstract could be published without any comment, which it does not need.

BERTHA KLIEN

LENS

THE FLUORESCENCE OF THE EYE LENS IN RATS AFTER LOCAL ROENTGEN IRRADIATION. A SPECTROPHOTOMETRIC INVESTIGATION

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Acta Ophth., 1959, *37:* 266–273

The fluorescence of the eye lens has previously been studied in experiments giving rise to cataract. Investigations of this kind seem not to have been made after irradiation, although roentgen cataract has been the object of detailed studies. Reports by various workers have established the connections between the roentgen dose, the course of the cataract, and the age of the animal. Generally it can be said that the time between irradiation with a cataractogenic dose and the appearance of the initial opacities, *i.e.*, the latent period, becomes longer the smaller the roentgen dose and the older the animal. Four stages are usually discernible: (1) the initial opacities occur around the thickened sutures of the posterior cortex and in the equatorial region; (2) they spread and confluate first in the posterior and then (3) in the anterior cortex, until finally (4) a mature cataract is formed. If fractionated irradiation is used a greater total roentgen dose is needed to cause cataract than if a single dose is given. With a single dose, a minimum of 800 r is required for 3-month-old rats, and more is usually given to produce a mature cataract.

Cataract developing without a sign of regression in any observed case was induced in rats by roentgen irradiation confined to one eye. In the incipient stage of the development of cataract, an increase in the fluorescence intensity was observed. In comparison with the nonirradiated control eyes this increase amounted to 17 per cent. At the mature stage, on the other hand, the fluorescence decreased by 31 per cent. Both the increase and the decrease could be considered significant, with P-values not exceeding 0.005. Only slight changes could be observed in the spectral distribution of the fluorescence. These were most pronounced in the mature cataract stage, in which the spectrum was displaced slightly towards the shorter wavelengths.

Whenever an attempt is made to explain a change in the fluorescence of the lens after the appearance of a cataract, a question arises as to the extent to which such a change may have been caused by the degeneration of the cells of the lens. In this connection, the present investigation is of interest, because a local cell injury was produced without affecting the general metabolism. From the results, it seems reasonable to assume that only a small increase in fluorescence can be caused by the physiochemical processes in the degenerating cells of the lens. The decreased intensity in fluorescence at stage 4 may have different

causes, but the simplest explanation is one that supposes a diluting effect caused by the absorption of fluid in the lens.

Comment: The described changes in the spectrograms of lenses topically irradiated with x-rays are of interest in view of the excellent techniques, the investigators employed and the availability of the ideal controls of lenses from the second shielded eye of the same animal. The mechanism underlying these changes cannot be evaluated, however, since in the rat the effects of such irradiation on the blood-aqueous barrier and on the water uptake of the lenses have not been studied up until now.

LUDWIG VON SALLMANN

RETINA

TETRAZOLIUM STUDIES ON THE RETINA

I. INTRODUCTION AND TECHNIQUE

TOICHIRO KUWABARA AND DAVID G. COGAN

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J. Histochem. & Cytochem., 1959, *7:* 329–333

The retina is a tissue of unusual interest for dehydrogenase studies because it has the highest reported rate of respiration of any normal tissue and will accumulate lactic acid aerobically as well as anaerobically to a degree equaled only by embryonic and neoplastic tissue. In a preliminary report, the authors noted what seemed to be two types of dehydrogenase distribution as delineated by tetrazolium precipitation (formazan). The papers in the present series contain a more detailed description of their findings based on a larger series of experiments using diverse substrates, different species, and other variables.

Portions of the retina were incubated for 3 hours at 37° C. with suitable substrates in the presence of tetrazolium. The tissues were then fixed in formalin, embedded in gelatin, sectioned in the frozen state, and examined without further staining. The reduction of tetrazolium visualized by the formation of an insoluble blue precipitate was taken to be an index of metabolic activity which in the presence of an adequate blank was in some way related to the substrate.

Full thickness portions of retina, and in some cases the entire retina, were incubated without freezing, cutting of sections, or dissection. This technique, made possible by the facts that the retina is only 0.5 mm. thick and can be easily separated from other tissues, yielded cytologic localization far superior to that obtained when cut sections were incubated as is the usual practice in tetrazolium

histochemistry. Not only did whole retinal pieces preserve the capacity for tetrazolium reduction better but the localization was more sharply confined to specific structures within the retina. Thus, the present experiments are thought to add importantly to the chemical studies of Lowry, Roberts, and Lewis (1956), whose retinal samples represented separate layers and could not be expected to give information on the heterogeneous activities within each layer or on the structural continuity of the layers.

With blue tetrazolium and suitable substrates, dehydrogenase activity is demonstrated in various, but characteristic, forms and places. A red color that depends on enzymatic activity is found in the reticular layers, nerve fiber layer, and lipid portions of the retina. This appears to represent a solubilization of reduced and partially reduced formazan in the lipid portions of the retina. The blue precipitate is found in mitochondria-like granules within certain cells, notably in the ellipsoids of the rods and cones, glial cells, Müller's cells, and to some extent in ganglion cells. It is also found as amorphous and rod-like crystalline deposits in the inner layers of the retina and as a fine dust-like deposit in the nerve fiber layer.

Metabolic activity in the retina as reflected by tetrazolium precipitation persists for hours after death and is present about equally in peripheral and central regions of the retina. The reduction brought about by the utilization of specific substrates representing intermediates in the major metabolic pathways will be the subject of subsequent papers in this series.

(Editorial comment by Dr. Albert M. Potts follows the third article in this series.)

TETRAZOLIUM STUDIES ON THE RETINA

II. Substrate Dependent Patterns

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J. Histochem. & Cytochem., 1959, 7: 334–341

In experiments designed to establish substrate dependent dye patterns, unsectioned retinas were incubated in a medium consisting of buffer, blue tetrazolium, and one of the following substrates: lactate, lactate-diphosphopyridine nucleotide (DPN), DPN, DPNH (the reduced form of DPN), and succinate. Control retinas incubated without substrate showed only an occasional reduction of tetrazolium, so slight as to be inconsequential.

With lactate as the sole substrate no appreciable reduction of tetrazolium occurred at neutral pH, but when DPN was added a constant pattern of pre-

cipitation occurred that was qualitatively the same in all species. This pattern was characterized by precipitation of tetrazolium in ganglion cells, Müller's fibers, and other glial cells. It was particularly obvious in human retinas and most particularly in pathologic retinas in which there was an accompanying gliosis. Another characteristic was the absence of activity in the ellipsoids of the rods and cones.

The lactate-DPN activity was somewhat enhanced by incubation anaerobically or with cyanide. It was completely inhibited by *p*-chloromercuribenzoate or by borate. It was not affected by prior blinding of the animal with iodoacetate, and section of the optic nerve affected it only by abolishing the activity in the ganglion cells.

When DPNH was used as a substrate the reduction of tetrazolium followed the same pattern. The inference is that lactate contributes the electron to DPNH and that tetrazolium reduction is effected through diaphorase. On the other hand lactate activity occurs at an alkaline pH (8.8 to 9.2) without the addition of DPN.

In contrast to the lactate-DPN system, succinate substrates showed predominant activity in the ellipsoids of the rods and cones and in inner portion of the retina unassociated with glial cells or ganglion cells. It was approximately equal in all species. The succinate activity was greatly decreased in pathologic retinas with associated gliosis. It was inhibited by cyanide and malonate but not by borate. Section of the optic nerve caused no appreciable change but prior blinding of the animal with iodoacetic acid led to a loss of activity from the rods and cones and a significant increase in activity in the inner retinal layers.

It is concluded that tetrazolium precipitation in the retina with lactate-DPN as a substrate is most marked in the glial cells and ganglion cells, whereas that with succinate as a substrate is most marked in the nerve fibers and in the ellipsoids of the rods and cones.

(*Editorial comment by Dr. Albert M. Potts follows the next article.*)

FURTHER OBSERVATIONS ON LIPID CRYSTALS IN TISSUE

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J. Histochem. & Cytochem., 1959, *1:* 67–68

Lipid crystals, variously interpreted as cholesterol or phospholipid, have previously been described in the brain cortex and in the retina. The crystals, birefringent and shaped like snowflakes, measured approximately 100 μ in length, and were readily soluble in organic solvents (except acetone), but were insoluble

in 0.1 N NaOH or 0.1 N HCl. The larger crystals were weakly sudanophilic. In the retina the crystals were noted to be present only in eyes which had been removed post-mortem and were not found in eyes enucleated during life and promptly fixed. The crystals apparently resulted from tissue changes that occurred after death and before fixation.

The crystals were not found in the optic nerve, cerebral white matter, or in liver, kidney, or other viscera obtained at the time of autopsy. It has now been been found, however, that crystals having similar morphologic and solubility characteristics can be induced in liver and other tissue under certain conditions of incubation. The formation of these crystals (apparently phospholipid) occurs concomitantly with sudanophilic fat formation in these tissues and is similarly affected by inhibitors, but the sites of crystal formation and fat formation are mutually exclusive.

The substrate in the liver from which the crystals arise is obscure, as is that for lipogenesis, but their reciprocal relationship suggests that both arise from the same substrate. It is, moreover, likely that both arise from the indigenous fat of the liver, which is normally present in the Kupffer cells, since this fat disappears on incubation coincidentally with the development of the sudanophilic or crystalline lipid. Formation of the lipid crystals occurs under conditions of unfavorable cell maintenance, while sudanophilic fat formation occurs under conditions which maintain the cells optimally.

Comment: All three reports describe in detail how the retina behaves in the now well known reaction with tetrazolium compounds. The colorless, soluble, oxidized tetrazolium is reduced by tissue dehydrogenase activity to a highly colored and insoluble formazan dye. As a first approximation the sites of dye localization correspond to sites of high dehydrogenase activity and by comparing retinas with added substrate with control retinas, one might hope to localize dehydrogenases for specific substrates.

However, the authors point out a number of possible reasons why these conclusions might not be completely valid. Since these considerations hold in some measure for all types of enzymatic histochemistry, the papers are worth perusing carefully for this purpose. The observations which show that lactate-DPN substrates cause greatest reduction in the area of Müller's fibers, and that succinate causes greatest reduction in the visual cell ellipsoids, are isolated findings. One looks forward to the day when similar well controlled studies by multiple techniques will summate to give an over-all picture of the metabolic activity of a retinal cell species.

ALBERT M. POTTS

RETINAL VEIN OCCLUSION

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New Zealand M. J., 1959, *11(Suppl.)*: 47–51

Some aspects of retinal vein occlusion are presented and illustrated with case histories.

Any of the following conditions may lead to retinal vein occlusion: (1) sclerotic degeneration of the wall of the vein, comparable to ordinary arteriosclerosis and characterized by proliferation of the endothelium and sometimes by detachment of parts of the endothelial lining; (2) sclerotic changes in adjacent tissues, especially of the central retinal artery and central connective tissue, which may reduce the lumen of the vein; (3) stasis of blood flow through the vein due either to these sclerotic changes, to carotid-venous fistula, to extreme exhaustion or marasmus, or to abnormal anatomy; (4) blood dyscrasias; (5) phlebitis, which may be either endophlebitis due to influenza or pneumonia or similar conditions, or periphlebitis due usually to tuberculosis; (6) trauma.

The question arises as to the cause of glaucoma following central retinal vein occlusion. The commonest theory is that the anoxic retinal tissue forms a cytotoxin or metabolite which inflames the angle of the chamber, leading to formation of vascularized membrane over the iris and angle. Other theories include (1) coincidental thrombosis of the choroid vessels; (2) blockage of the angle by albuminous intraocular fluid; (3) turgescence of the vitreous due to absorption of hemorrhage. In our patient (see Robinson's third case) two factors seem to have operated: first, the thrombosis of the vorticose veins led to engorgement of the ciliary body; second, intense congestion of the conjunctiva and sclera contributed to obstruction of the aqueous veins. The rubeosis seems to originate in simple venous obstruction rather than in any cytotoxin, at least in patients with carotid-cavernous sinus fistulas.

A few cases of retinal vein occlusion have been noted in cases of polycythemia, multiple myeloma, and thrombocythemia. Trauma has been rarely implicated, but one of our patients developed central vein thrombosis 2 days after striking her eye in an automobile accident.

The use of anticoagulants as treatment of these cases is controversial. Five of our patients were treated with them and five were not; in each group one was improved and four were not. So far there is no conclusive evidence that anticoagulants prevent recurrences. The author believes that once the thrombus if formed, anticoagulants have little effect, but they may be useful in preventing or retarding thrombosis in some of the smaller vessels. The danger of hemorrhage following anticoagulant therapy should be borne in mind, but does not outweigh the probable benefits.

Comment: As the author emphasizes, the greatest value of anticoagulant therapy in

venous occlusive disease lies in the possibility of delaying or preventing complete occlusion. If it cannot be prevented, as in relentlessly progressive sclerotic disease, the delay may be sufficient to permit formation of compensating anastomotic channels. Such collaterals may become evident from 3 to 14 months after impairment of the venous circulation has set in; any incomplete occlusion of the central retinal vein, therefore, calls for long-term anticoagulant treatment.

BERTHA KLIEN

MICRO-ANEURYSMS OF UNKNOWN NATURE OBSERVED OPHTHALMOSCOPICALLY

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Acta ophth., 1959, *37:* 279–289

Ballantyne and Lowenstein in 1943 and 1944 (Tr. Ophth. Soc. United Kingdom *61:* 95–115 and Brit. J. Ophth., *28:* 593–598) demonstrated histologically that the ophthalmoscopically observable "punctate haemorrhages," sanguinolate spots occurring particularly in the posterior pole of the retina of diabetes mellitus patients are microaneurysms arising from the venous capillaries.

Microscopically these aneurysms manifest themselves as compact spherical or ovoid masses of erythrocytes, each enveloped in a membrane and communicating with a neighboring capillary. They vary in size from 20 to 100 microns.

Ophthalmoscopically they are seen as well defined, small, round blood spots, in contrast to small hemorrhages, which are the same size or little larger, but irregular of shape with blurred outlines. Unlike punctate hemorrhages, which may be absorbed within a few weeks, microaneurysms remain unchanged for months or years.

Although the occurrence of a single or a few microaneurysms in the central part of the fundus is generally regarded as one of the earliest unequivocal signs of diabetic retinopathy, cases of microaneurysms of nondiabetic origin have been reported in the literature associated with other generalized diseases such as hypertension and anemia and in relation to local fundus changes. The review of the literature revealed no descriptions of ophthalmologically observed retinal microaneurysms in healthy persons with otherwise normal fundi.

In an investigation on the conjunctival vessels of diabetics, the author submitted 30 nondiabetics, as a control series, to very careful opthalmoscopy and found two perfectly healthy individuals who each had one sanguinolent spot in one eye of the same appearance as microaneurysms in diabetic retinopathy. In addition, a patient examined in the eye department as part of a general examination owing to a complaint of headache, presented two sanguinolent spots in one eye. She did not suffer from diabetes mellitus.

Except for 1.25 emmetropia of both eyes in one, the two control subjects presented no other abnormalities on ophthalmoscopic, slit lamp, general somatic and complete blood and urine examinations. The oral glucose tolerance test was normal in both. No alterations of the saguinolent spots were noted 6 and 4 months later.

The patient admitted for headache was found to be suffering from iron deficiency anemia due to considerable blood loss involved in menorrhagia over a period of 6 or 7 years. In addition to the sanguinolent spots in the left eye, a few sharply outlined white spots were scattered among the vessels of both eyes. Intramuscular injections of Imferon, 2 ml. daily, were continued for about a month. Abrasions of the uterine mucosa, done about a month later, resulted in normal menses. Ophthalmoscopy 6 months later showed unchanged conditions in the right eye. In the left the sanguinolent spots had disappeared. It was also impossible to identify any of the scattered white spots (still present in both eyes) as the previous microaneurysms in a hyalinized state. As microaneurysms may undergo spontaneous hyalinization in the course of time, it is hazardous to attach etiologic importance similtaneously with the cure of the anemia.

In the first 2 cases, the aneurysms must be supposed to be of a congenital character as they were found in healthy individuals with no signs of past or present local or generalized diseases.

Comment: Increasing experience in the clinical use of percutaneous renal biopsy and in the interpretation of electronmicroscopic findings (Arnold and Spargo, Circulation, *19:* 609, 1959, and Arnold *et al.*, Tr. A. Am. Physicians, *71:* 186, 1958) are changing our concept of the sequence of events in diabetes mellitus.

The intracytoplasmic change in the endothelial cells which is the precursor of the Kimmelstiel-Wilson lesion can be demonstrated with the electronmicroscope before overt diabetes develops, and one must conceive of the possibility that diabetic lesions in other organs, including the retina, may have their beginning also at an earlier stage than heretofore thought, and might become clinically visible before other obvious signs of diabetes have occurred.

BERTHA KLIEN

RETINAL GROOVES CAUSED BY PRESSURE ON THE GLOBE

NIELS VEDEL-JENSEN

Acta ophth., 1959, *37:* 59–64

The subject of retinal grooves or folds produced as a characteristic ophthalmologic picture due to pressure on the globe resulting from retrobulbar expanding lesions has attracted interest in the past. In addition to the 9 previously reported cases uncovered in the literature, the author reports two of his own. These typical retinal grooves are found most commonly between the disk and

the macula and, in the histologic report of Wolter and Jampel, two types of grooves were distinguished: (1) large folds involving all the layers of the retina and the choroid, and (2) fine grooves localized in the internal limiting membrane and the nerve fiber layer. Wolter and Jampel concluded that the retinal folds arise on a mechanical basis as a result of prolonged permanent pressure on the globe from a retrobulbar mass.

The author describes one girl with unilateral exophthalmos with the globe displaced outward and downward. Fine parallel reflex striations were seen over the entire fundus gradually disappearing in the periphery which ran obliquely temporally and which were most pronounced about the macula. The tumor was found to be a malignant hemangiosarcoma which required exenteration. In the histologic sections, the eye itself was completely normal. It was impossible to demonstrate the retinal grooves seen clinically. The negative histologic findings suggest that the process of groove formation is reversible when pressure on the globe is removed, as it was during surgery in this case.

The second patient had orbital cellulitis from pansinusitis with pronounced unilateral exophthalmos. Again fine parallel vertical striations were seen and, after 18 days, these lines completely disappeared with normal fundus found on the 21st day after treatment.

In contrast to some of the previous cases reported in the literature, the easy reversibility of the retinal folds in these cases was concluded to be due to the relatively short time that the abnormal pressure had been operating on the globe. It is also possible that the young ages of these patients had some significance. In the more severe cases with greater deformation of the globe and more prolonged pressure, all the layers of the retina may be involved as described by Birch-Hirschfeld and Lohlein. However, the authors feel that in the majority of cases the histologic changes in the retinal groove formation appeared to be localized to the internal limiting membrane and the nerve fiber layer.

Comment: The author is in agreement with previous writers that the earliest changes of this pathologic condition involve the inner layers of the retina and may well be transient, particularly if retro-orbital pressure is lowered by surgical intervention. However, if the changes persist for a period of time, the more permanent, darker, and deeper corrugations involving all the retinal layers appear, and these may persist for long periods of time as has been emphasized in a recent report by Hedges and Leopold. They reported two cases in both of which prolonged retro-orbital pressure accounted for broad permanent retinal folds. Vedel-Jensen believes in Lohlein's contention that the condition develops only if the globe is compressed from above downwards, pressing the globe against the unyielding bony orbital wall. This was not the case in two cases reported by Hedges and Leopold and therefore it is obvious that, if the lesion is in the immediate retrobulbar space or in a favorable position elsewhere in the orbit, it does not necessarily have to press from any particular quadrant in order to produce this pathologic finding. The author even goes further in stating that, when the globe is compressed in the vertical plane, the corresponding compression of the retina takes place in the same plane while at the same time stretching or tension develops in the horizontal plane. The important fact is that pressure must eventually be everted in the immediate retrobulbar space.

It may therefore be concluded that the histopathology and clinical findings of parallel

retina folds as evidence of retro-orbital expanding lesions has been well documented in the literature and is due not only to retrobulbar mass lesions but also to exophthalmos associated with thyroid abnormalities as reported by other authors.

THOMAS R. HEDGES

DIETARY FATS AND THE DIABETIC PATIENT

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J.A.M.A., 1959, *261:* 431–434

It is noted that, among other complications arising from the diabetic state, there is a predisposition to a form of vascular disease of the eyes and kidneys. In the eye this condition goes on to retinitis proliferans, widespread hemorrhage and eventual destruction of the eye. A study was undertaken to determine whether these diseases are related to qualitative or quantitative abnormalities of the diet, and whether any specific dietary modifications will result in prevention of such abnormalities or improvement in existing disease.

Diets containing relatively large amounts of polyunsaturated fat, modest amounts of carbohydrate, adequate amounts of protein, and limited amounts of saturated fat are stated to be associated with normal levels of blood lipids. Prophylactic and therapeutic values in regard to atherosclerosis and diabetic retinopathy-nephropathy are hoped for by maintenance of such lipid levels.

The possible types of diet for the diabetic patient are considered, and three factors emerge as necessary in the structure of a diet: acceptability of the diet to the patient, optimal balance between diet and a single daily dose of long-acting insulin in terms of avoidance of hyperglycemia and hypoglycemia, and the maintenance of the lowest possible level of plasma compatible with the other two considerations.

Table 1 shows the diets employed in the study.

The Group I diet had poorest patient acceptance and was used only in cases of extreme vascular disease and elevated blood lipids. Maintenance of satisfactory cholesterol and total lipid levels led to transfer to the Group II diet. Normal plasma lipid levels for 4 to 6 months led to transfer to the Group III diet.

The Group I-A diet is said to be more palatable than the Group I diet, and proof of its effectiveness in reducing plasma lipid levels would lead to its replacing of the Group I diet.

TABLE 1
*Résumés of Various Diets**

2000-calorie Diet	"Group I" Diet	"Group I-A" Diet	"Group II" Diet	"Group III" Diet	Routine Diets for Diabetes
Daily use:					
Nonfat milk	980 ml.	490 ml.	600 ml.	250 ml.	980 ml.
Low-calorie cottage cheese	130 gm.	100 gm.	100 gm.	Included in Group 1 meats	Included in Group 1 meats
Group I meats†	None	90 gm. (fish only)	120 gm.	120 gm.	90 gm.
Group II meats‡	None	None	None	120 gm.	90 gm.
Safflower, corn, cotton or soy oil	60 ml.	60 ml.	60 ml.	60 ml.	30 ml.
Butter or margarine	None	None	None	None	15 gm.
Nuts—50% as walnuts	65 gm.	65 gm.	65 gm.	65 gm.	65 gm.
Low-fat bread exchanges	4	5	4	4	3
Fruit exchanges	4	5	4	4	3
Vegetable—A list	Ad lib.	Ad lib.	Ad lib.	Ad lib.	Ad lib.
B list	2	2	2	2	2
Protein	80 gm.	83 gm.	94 gm.	89 gm.	104 gm.
Fats	100 gm.	105 gm.	105 gm.	119 gm.	106 gm.
Carbohydrates	190 gm.	182 gm.	170 gm.	144 gm.	159 gm.
Linoleic acid§	48	48	48	48	34
Linoleic acid¶	60	60	60	60	40

* Meal plan is to use 3 regular meals with midmeal feedings consisting of nonfat milk and nuts.

† Group I meats (7% fat or under). 1 exchange = protein, 7 gm.; fat, 2 gm.

Low-calorie cottage cheese—3 tbsp.

Fowl, fish, shellfish or liver—1-oz. portion.

‡ Group II meats include remainder of regular meat-exchange list, such as beef, veal, lamb, pork, cheddar-type cheese and egg.

1 exchange = protein, 7 gm.; fat, 5 gm.

§ Approximate linoleic acid if corn, cotton or soy oil used, walnuts supply 50% of nuts and other nuts make up remainder.

¶ Approximate linoleic acid if safflower oil is used and the same nuts as in part § eaten. Linoleic acid in other foods not included in estimate.

Comment: This paper is by one of the leaders in the current trend toward attempting to prevent or arrest the vascular complications of diabetes by dietary means. The present paper gives details of diets of various degrees of fat restriction (and patient acceptance). It is of particular interest to the internist responsible for the patient's diabetes, especially when he is asked by the ophthalmologist to restrict the patient's dietary intake of fat.

BERNARD BECKER

THE EFFECT OF A LOW FAT DIET ON THE SERUM LIPIDS IN DIABETES AND ITS SIGNIFICANCE IN DIABETIC RETINOPATHY

W. F. Van Eck

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Am. J. Med., 1959, *27:* 196–211

Although the literature on the influence of dietary fat and cholesterol on the serum lipids is abundant, little attention has been given to the significance of dietary fats in diabetes mellitus and its complications. Yet the caloric loss due to reduction of carbohydrate in the diet has been regularly balanced by increasing the fat, which today amounts to between 80 and 110 gm. daily. Atherosclerosis seems to be commoner among diabetics than among the normal population, and, at least in poorly controlled diabetes, serum lipids are increased. A low fat diet has been advocated, but observations of its effects on serum lipids or cholesterol levels have been only incidental. Also analyses of serum lipids in diabetics have been made on fasting patients without records of daily fluctuations.

Therefore a study of diurnal variations in serum lipids and cholesterol levels and of the effects of fat intake on these patterns has been carried out on 12 patients with diabetes; 11 kept to the diet for 6 to 24 months. All were on caloric balance, and in all diabetes was controlled either by diet or by insulin. All had some degree of retinopathy.

After preliminary serial serum-lipid studies, the patients were placed on a diet containing less than 20 gm. of fat daily, and 80 to 110 gm. of carbohydrates were added. Serial lipid studies were obtained at 3-, 6-, and 12-month periods, aboratory studies were carried out at various intervals, and color photographs were taken of the fundi at the beginning of the study and afterwards at 3-month intervals. Four patients had hypertension and most showed some signs of peripheral arteriosclerosis. These and other clinical and laboratory observations were little changed during the study. All were able to replace the carbohydrates by fats by first stopping the fats and then gradually increasing the carbohydrates. This was accomplished without increasing insulin.

Others have noticed that diabetics increasingly utilize carbohydrates as they increase their ingestion. In two studies with fat as low as in ours, an increase in glucose tolerance similar to that in our cases has been observed. Our patients tolerated up to a 135 gm. increase in carbohydrates.

Charts based on hundreds of diurnal changes have led to certain observations. Serum cholesterol and cholesterol fractions changed more or less in proportion, but cholesterol esters comprised a lower percentage, and total cholesterol dropped consistently an average of 20 per cent. Exceptions occurred only when patients neglected the fat restrictions of the diet. In general, those with either elevated serum or triglyceride fractions showed decrease in the elevated factor on the

low fat diet. The amount of fat ingested and absorbed itself appeared to play a part in regulating serum lipid levels.

Photographs of fundi showed that exudates of various degrees regressed in 8 of 10 patients, with complete disappearance of two very large exudates and marked improvement in three others. In only one patient antiopathy, manifested by neuroaneurysms and hemorrhages, improved.

A low fat diet seems worth considering in diabetics with elevated serum lipids and distinct retinopathy.

Comment: One of the more attractive hypotheses for the pathogenesis of diabetic retinopathy concerns itself with the role of circulating lipids. This is based on clinical studies as well as animal experiments (Wilens; Hartroft and co-workers; etc.).

Recently a number of clinics have attempted to treat or prevent diabetic retinopathy and Kimmelstiel-Wilson disease with low fat diets. Although in the experience of most investigators this has proved unsuccessful, remarkable improvements in some diabetic patients have been reported by the use of such rigid low fat, low sodium diets as the rice diet (Kempner, 1958; see SURVEY, *4:* 629, 1959).

The present report concerns the use of a 20-gm. fat diet. This was effective in lowering serum lipids and in decreasing the exudates seen in the retina. However, it was much less effective in altering or preventing capillary aneurysms and hemorrhages.

Newer and more effective means of decreasing blood lipid levels are becoming available. It would be of considerable interest to study the effect of these agents on the progression of diabetic retinopathy. Because of the variability of the disease, "double-blind" experiments are needed.

BERNARD BECKER

GLAUCOMA

STUDY OF THE FREQUENCY AND DISTRIBUTION OF GLAUCOMA

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J.A.M.A., 1959, *171:* 1090–1093

Because of its obscure etiology, no specific preventive measures for glaucoma are known except for early diagnosis. The tonometer procedure is applicable to mass screening of population groups, but the procedure has not come into widespread use. It is suggested that tonometry might be practiced more extensively if information were available as to which segments of the population are most

prone to glaucoma, thus making possible selective testing programs. Inherited predisposition and age are recognized as factors predisposing to glaucoma, but it is felt that other factors, especially the discovery of a significant statistical association between glaucoma and other diseases, are needed to assist in case-finding.

The article presents information regarding the frequency and distribution of previously unrecognized glaucoma among various population groups obtained from a glaucoma detection program in which 13,155 persons were tested. It is felt that the difference between some groups in the frequency of occurrence of glaucoma is statistically significant.

Tonometer tests were routinely applied to persons over 40 in three categories: (1) applicants for employment health cards, primarily Negro women in domestic service; (2) new admissions to the clinics of the outpatient department; and (3) patients attending the ophthalmology clinic, who are not included in the total figures.

Persons showing an intraocular tension of more than 25 mm. Hg with the Schiøtz tonometer were referred to the ophthalmology clinic for further study. There, hypersecretion and narrow angle mechanisms were studied by tonometry and gonioscopy in arriving at an evaluation.

Suspects were categorized as follows: (1) Glaucoma, on the basis of persistent abnormalities of intraocular tension, diurnal variation in intraocular tension, difference of 5 mm. Hg or more in intraocular tension between the two eyes, and positive water provocative or other provocative tests. (2) Borderline glaucoma, on the basis of two abnormalities. (3) Doubtful cases, on the basis of one abnormal finding.

The highest incidence of glaucoma (Table 1) was found in those attending the ophthalmology clinic. The high frequency of glaucoma reported in persons over 60 in a hospital for the aged is said to indicate the strong influence of age on the frequency of occurrence of the disease, as does the low rate in persons under 40. A high rate of discovery was also seen in females (both Negro and Caucasian) visiting outpatient clinics (Table 2). Negro males engaged in occupations involving considerable manual labor with minimal demands on discriminatory vision

TABLE 1

Frequency of Glaucoma in Various Groups

Group	Persons Tested	Persons with Glaucoma	
	no.	*no.*	%
Employment health card applicants	2,516	45	1.8
Outpatient clinics	4,742	138	2.9
Shelby County Hospital	562	36	6.4
Nonhospital groups, total	5,335	52	1.0
Under 40 years	(1,027)	(2)	0.2
Over 40 years	(4,308)	(50)	1.2
Total	13,155	271	2.1
Ophthalmology clinic	902	62	6.9

TABLE 2

Distribution of Glaucoma by Race, Sex, and Occupation in 11,566 Persons over 40 Years of Age

Group	Caucasian						Negro					
	Male			Female			Male			Female		
	Tested	Glaucoma		Tested	Glaucoma		Tested	Glaucoma		Tested	Glaucoma	
	no.	*no.*	%	*no.*	*no.*	%	*no.*	*no.*	%	*no.*	*no.*	%
Employment health card applicants	153	0	0.0	515	7	1.4	316	6	1.9	1,532	32	2.1
Outpatient clinics	319	4	1.3	320	11	3.4	1,733	43	2.5	2,370	80	3.4
Teachers and department store employees	79	0	0.0	817	0	0.0	55	0	0.0	204	2	1.0
Other occupations	1,704	21	1.2	598	2	0.3	811	25	3.1	40	0	0.0
Total	2,255	25	1.1	2,250	20	0.9	2,915	74	2.5	4,146	114	2.7
Ophthalmology clinic	116	3	2.6	133	2	1.5	216	21	9.7	437	36	8.2

TABLE 3

Associated Disease in 151 Persons with Glaucoma Discovered by Detection Program

Disease	Outpatient Clinics (104 Persons)		Employment Health Cards (47 Persons)	
	no.	%	*no.*	%
Arteriosclerosis	66	63.5	13	27.7
Hypertension	52	49.0	10	21.3
Arthritis	28	26.9	8	17.0
Syphilis	20	19.2	7	14.9

also showed a high frequency of occurrence of glaucoma. The lowest frequency of subclinical glaucoma was found in Caucasian females engaged in occupations requiring discriminatory visual activity.

Table 3 shows the occurrence of other diseases in persons with subclinical glaucoma detected by the program. It is felt that the high incidence of such associated disease raises the possibility of common underlying mechanisms in the pathogenesis of the associated diseases.

It is felt that the information derived from this study will aid in establishing selective case-finding procedures. It is suggested also that tonometry should be an indispensable procedure in the examination of persons over 40, and most especially of those with chronic illness.

Comment: The over-all incidence of elevated intraocular pressure in this series (1 to 2 per cent) agrees well with previously reported studies. It again emphasizes dramatically the important public health problem presented by glaucoma. The prevalence reported would be even higher had the authors chosen a lower pressure limit for referral. At the level they chose (25 mm. Hg) one is able to detect less than 50 per cent of patients with proved glaucoma.

BERNARD BECKER

CLINICAL APPLICATIONS OF TONOGRAPHY AND DIURNAL VARIATION IN OCULAR TENSION TO EVALUATION OF GLAUCOMA OPERATION

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Yonago acta med., 1959, *4:* 45–56

The method for the clinical measurement of the outflow of aqueous humor, which was named tonography, is clinically important not only as the early diagnostic method in the detection of glaucoma and the evaluation of treatment of glaucoma, but also as a tool for the choice in the mode of operation for glaucoma. Diurnal variation in ocular tension is an accepted method essential to early diagnosis of glaucoma. The present article reports on the findings of tonography and the diurnal variation in ocular tension before and after every method of the operation of glaucoma, with accompanying case reports.

Of 11 eyes with chronic simple glaucoma, 14 with congestive glaucoma, 5 with secondary glaucoma, and 3 with aphakic glaucoma, 6 eyes were operated by cyclodialysis, 16 by trephination, 7 by Wheeler's operation, 3 by intracapsular lens extraction with inferior approach, and 3 by anterior sclerotomy. For these eyes and 6 case reports, tonographic results and diurnal variations in ocular tension were studied before and after operation, and were employed for the evaluation of the effect of operation or re-operation.

The facility of outflow was improved with operation in all kinds and by all operations of glaucoma, but differed in degree and duration of restoration in every kind and every mode of operation of glaucoma. The improvement of outflow facility when it was only a short time after operation, was more marked in congestive glaucoma than in chronic simple glaucoma. In a comparison between acute and chronic congestive glaucoma, the recurrence of damage in outflow facility predominated in acute congestive glaucoma. In chronic congestive glaucoma, improvement of C-value was excellent within and over 2 months after operation. It might be allowed to say that glaucoma must be operated in the prodromal stage without acute attack.

Generally speaking, in chronic simple glaucoma and chronic congestive glaucoma, the examined factors were well restored to normal by operation. On the other hand, if no improvement appeared in the examined factors 2 months after the first operation, reoperation was recommended without hesitation in order to improve these factors and to achieve perfect cure of the glaucoma. Cyclodialysis was applied only to chronic simple glaucoma. This resulted in a well improved C-value within 2 months after operation, but, as time went on, the effect tended to decrease.

Trephination was applied to many types of glaucoma in the present experiment, with the exception of aphakic glaucoma. It was recognized as an excellent

method for glaucoma; trephination in general was found to produce the greatest increase in facility of outflow. Wheeler's operation was found to produce the greatest increase in C-value in a short time after trepanation; this procedure might well be recognized to be effective for glaucoma with high tension.

As to the relation between the diurnal variation in ocular tension and operation for glaucoma, there were many cases in this series where the diurnal variation in ocular tension diminished with operation. This suggested again that in glaucomatous eyes with greater diurnal variation in ocular tension, local change of the eye is closely related to the exaggeration of the diurnal variation in ocular tension.

A few eyes, in which high tension had remained after a first operation and which could not be restored or soon relapsed despite re-operation, in diurnal variation as well as in facility of outflow, might be cases of malignant glaucoma.

Comment: It is difficult to evaluate tonography in successfully operated glaucomatous eyes after cyclodialysis and filtering operations. First of all the tension early may be extremely low after cyclodialysis if aqueous secretion is temporarily diminished. Similarly if a large filtering cicatrix is present after a filtering operation the tension is low and falls quickly. The facility of outflow has no relation then to the trabecular meshwork but only to the direct exit flow which depends on many mechanical factors. The only conclusion one might draw is that certain operations tend to make bigger filtering scars while others result in less filtration. We know clinically that trephine blebs when successful have a greater tendency to filter because of the thinner bleb covering.

Emphasis is placed on the difference in outflow facility after operation for congestive glaucoma as compared to simple glaucoma and early in the postoperative period as compared to later. Here again the results would depend on the clinical picture. In a case of angle-closure glaucoma the results would depend more on the condition of the angle than on the presence or absence of filtration. If a peripheral iridectomy or even a filtering operation which does not filter is done and the angle is open, the aqueous outflow is normalized through normal trabecular channels. On the other hand if synechias are present, the outflow will depend entirely on the functioning of the bleb. It is difficult to understand how significant conclusions can be drawn in regard to the outflow.

SAUL SUGAR

NEURO-OPHTHALMOLOGY

ASSOCIATED MOVEMENTS IN ANESTHESIA: THE WINKING-JAW PHENOMENON

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Anesthesiology, 1959, *20:* 585–586

The winking-jaw phenomonen is an associated movement characterized by a contralateral horizontal displacement of the jaw following corneal stimulation during light anesthesia. We have examined 1,017 patients under light thiopental nitrous-oxide anesthesia and have found this phenomenon present in 37.6 per cent. It was present in 41.5 per cent of the males and 31.3 per cent of the females, with lowest incidence in infancy and the elderly.

The characteristics of this phenomenon are: (1) It disappears when anesthesia deepens beyond the first plane of the third stage. It is chronologically inseparable from the corneal reflex, and when present, stimulation of the cornea provokes a simultaneous appearance of the phenomenon. (2) It is subject to fatigue following repeated stimulation. (3) It is usually bilateral. (4) Normality of muscular tone is optimal for the phenomenon. Excessive muscular contraction or curarization interferes with its appearance. (5) The stronger the closure of the eyelids in response to corneal stimulation, the more prominent the winking-jaw phenomenon.

The phenomenon should be classified as faciotrigeminal, palpebromandibular, or orbiculopterygoid synkinesis involving an associated movement between muscles innervated by the facial nerve and those by the trigeminal nerve (homolateral external pterygoid). The phenomenon was first observed in patients with organic lesions of the encephalon.

It is obvious that the functional changes in the central nervous system induced by the anesthesia are capable of duplicating physiopathologic situations which are the basis of associated movements represented by the winking-jaw phenomenon.

It is not clear as to what importance the winking-jaw phenomenon has. It is, however, additional evidence of the effect anesthesia may have upon the central nervous system in a different direction than is usually considered. More information is needed on the difficult problem of assaying response to anesthesia.

RETROBULBAR NEURITIS

Report of 57 Cases

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Chinese M. J., 1959, *79:* 55–58

From January 1951 to June 1955, 57 cases of retrobulbar neuritis were seen at the College hospitals, 4.4% of 1,301 hospitalized ophthalmologic cases during that period. In China the disease is preponderant in males; of the 57 cases there were 44 males (79%) and 13 females. Forty-eight of the cases were in the 15- to 29-year age group.

This apparent predilection for the most active period of life is worth noting. There were 19 acute cases (33.3%) and 38 chronic ones (66.7%). Fifty-two cases were bilateral (91.2%), totaling 109 eyes. In the majority of cases of retrobulbar neuritis seen in China the etiology was unknown; in the present series all patients were given detailed physical, laboratory, and ophthalmic examinations. In this series 34 cases showed definite signs of causal relation between other diseases and retrobulbar neuritis. In a large number (45.8%) focal infection appeared to be responsible.

Therapy was adapted to the different causes; in most cases it was combined. Among the main forms of treatment, opening of the ethmoid sinus, fever therapy and penicillin administration were beneficial. Ethmoidectomy usually produced dramatic results, especially in acute retrobulbar neuritis.

Comment: This article is of interest in that it reviews the previous Chinese literature on optic neuritis as well as a current series. Interesting facts noted include a preponderant

Table 1

Age Distribution

Age Group	No. of Patients
yr.	
1–4	1
5–9	0
10–14	0
15–19	17
20–24	19
25–29	12
30–34	2
35–39	1
40–44	1
45–50	2
Over 50	2

TABLE 2
Results from Different Methods of Treatment

Treatment	Causal Factors	Cure	Marked Improvement	Slight Improvement	No Change	Worse	Total
Opening of ethmoid sinuses	Ethmoid sinusitis			2			2
	Normal sinus	9	9	12	8	2	40
Fever therapy	Focal infections	2	3	1			6
	Unknown cause	6	4	3	7	3	23
Penicillin injection	Focal infections	3		3			6
	No focal infections	6	5	3	5	2	21
General treatment	Known cause			1	1	1	3
	Unknown cause				2		2
Tonsillectomy	Chronic tonsillitis	2					2
Antiluetic treatment	Syphilis			2			2
Aureomycin	Neuromyelitis optica			2			2
Total		28 (25.7%)	21 (19.3%)	29 (26.6%)	23 (21.1%)	8 (7.3%)	109

incidence of retrobulbar neuritis in males rather than females, with the highest age incidence between 15 and 29 years. Despite this fact the incidence of multiple sclerosis was almost nil in the total reviewed series—2 cases in 426 reported instances of retrobulbar neuritis. In the series presented by the author the cause was unknown in 40 per cent but in the remainder, focal infections were thought to be at fault. Interestingly, opening of the ethmoid sinuses was of important therapeutic help, even though there was no sinusitis in the majority—an effective way of augmenting the patient's own corticosteroids by way of stress.

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IS LUMBAR PUNCTURE HARMFUL IN MULTIPLE SCLEROSIS?

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J. Neurol. Neurosurg. & Psychiat., 1959, *22:* 238

That lumbar puncture is detrimental in multiple sclerosis has been taught for many years. More recently, during the Sixth International Neurological Congress, held in Brussels in July, 1957, Professor K. Henner stated firmly that lumbar puncture was contraindicated in the disease (Excerpta med., Sect. VIII, 1957, *10*, Congress issue, p. 40).

During a current survey of cases of multiple sclerosis in northeastern England, during which 700 patients were interviewed and examined, it was found that rather less than half had been subjected to spinal puncture; in 250 cases the information was considered sufficiently reliable for analysis. Of these, 231 patients reported their condition as unchanged, 14 patients reported improvement, and 5 patients considered that their condition had deteriorated. In many instances this subjective information was authenticated by a record of objective findings. For what such inquiry is worth, it lends little support to the view that this procedure significantly affects the course of the disease.

A second phase of the inquiry involved a comparison in 100 cases of the apparent course of the condition during the month following lumbar puncture with the tempo of progression evident during similar periods 12 months earlier and 12 months later. Of these 100 patients, in 81 there was no difference; in 19 cases significant differences were noted. One patient showed very marked deterioration following lumbar puncture; 8 patients improved during the following month, and 10 patients showed no definite change during the month following lumbar puncture, while in the previous period eight of them had been deteriorating.

The results indicate that lumbar puncture has little effect on the course of multiple sclerosis, and that any apparent effect occasionally observed is as likely to be favorable as deleterious. The risks of overlooking clinically atypical compression of the spinal cord are well known. There is clearly no reason to withhold the procedure in any case where the faintest suspicion of such a lesion occurs.

Comment: The possibility that lumbar puncture may be harmful in a patient with multiple sclerosis is a novel idea to the editor, and a brief survey of the major neurologic sources in this country finds no mention made of this. In the volume of *Multiple Sclerosis and the Demyelinating Diseases* published by the A.R.N.M.D. in 1950, there is a brief mention in the discussion of a paper of the fact that spinal anesthesia may be contraindicated in multiple sclerosis. It is comforting to know that the author feels that lumbar puncture has little effect on the course of multiple sclerosis.

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OCULO-PALPEBRAL MANIFESTATIONS OF MUCOUS MYELINIC NEUROMA

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Arch. opht., 1959, *19:* 257–269

Tumors of the peripheral nerves with palpebral, conjunctival or corneal localization are very rare. They are almost always manifestations of Recklinghausen's disease and, more specifically, of the classical plexiform neuroma in its orbital or palpebral site. Aside from this affection, only neurinomata and ganglioneuromata, rarely observed, are known as nervous tumors.

The present study is based upon 2 cases, one observed at the Dermatological Clinic, and the other at the Ophthalmological Clinic of Toulouse. Only one similar observation has been reported by Froboese in 1923, in a boy 12 years of age.

In these 2 cases, in young patients, the syndrome was characterized by: (1) the presence of myelinic neuromas localized on the conjunctival, labial, lingual, pituitary and laryngeal mucosa; (2) hypertrophy of the corneal nerves; (3) constitutional anomalies: centrofacial lentiginosis and cranial malformation; (4) absence of cutaneous, neurologic or osseous manifestations of Recklinghausen's disease.

This clinical entity poses difficult problems from a diagnostic, anatomopathologic, pathogenic and nosologic point of view. The centrofacial disposition of the neuromas and of the lentiginosis as well as the osseous cranial malformations point to a possible dysraphic congenital nature of the affection. While there is a relation to Recklinghausen's disease, mucous myelinic neuroma constitutes a distinct nosologic entity.

As to a differentiation from Recklinghausen's disease, the latter may show identical clinical and anatomical lesions in its palpebroconjunctival manifestations; the presence of the corneal nerves has been especially pointed out. In certain forms even the same histologic characteristics may be present. But the mucous and not cutaneous location of the neuromas, their unique cephalic topography, symmetrical and median, the centrofacial lentiginosis, the cranial osseous modifications are characteristics of the mucous myelinic neuromatosis which are not found in Recklinghausen's disease. On the other hand, the diffuse irregular and particularly cutaneous location of the nervous tumors, and the cutaneous, nervous, and osseous signs are characteristics of neurofibromatosis which do not appear in the observations of the present study.

As to a comparison with neurinomas, the tumor is unique and voluminous and no corneal manifestations are found. The histologic aspect is entirely different. Similar conjunctival and corneal manifestations may be observed in the ganglioneuromas. The association, however, of a suprarenal tumor of the type of a pheochromocytoma with the ocular manifestations, which appears as paroxysmal

arterial hypertension in the patient, characteristic of ganglioneuroma, is not observed here. Most mucous neuromas have a labial or lingual location.

We are dealing with mucous neuromas whose site is in the subepithelial chorion. This location is an important characteristic which differentiates these neuromas from cutaneous neuromas. The latter are acquired tumors, usually found in adults and are painful. The preservation of the myelinic sheath of the nervous fibers and the absence of ganglionic cells are two additional essential characteristics. The possibility of traumatic origin may be disregarded. A regular and well ordered disposition such as we have observed would be hard to explain after microtraumatism. Besides, never was the slightest inflammation to be observed in the corneal manifestations.

It is too early to come to definite conclusions as to the course of the affliction. The affection has remained stationary in both cases for a number of years. It may be subject to recurrence after excision, though none has been observed in the present cases, in the course of 1 year.

BILATERAL LOSS OF VISION COMPLICATING MITRAL STENOSIS

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Med. J. Australia, 1959, *II:* 185–187

Bilateral loss of vision resulting from cerebral infarction is uncommon. To the 58 cases presented in a recent survey by Symonds and MacKenzie, 49 of which were from the literature, the authors now add another, that of a 48-year-old man with rheumatic heart disease. He was admitted to the Brisbane Hospital about 2 hours after a sudden and simultaneous loss of vision in both eyes. Accompanying the loss of sight, he experienced severe pain in the right retro-orbital, right frontal, and occipital regions. This was associated with giddiness and vomiting, and although consciousness was not lost, he felt dazed and confused.

Except for three previous attacks of rheumatic fever, his medical history was not relevant; in particular he had never before suffered from a similar illness and had no previous history of visual upset. A diagnosis of rheumatic mitral stenosis, atrial fibrillation, and occipital lobe infarction due to embolism was made. Anticoagulant therapy was started on March 20, some 30 hours after the onset of the acute illness. On March 21, 2 days after the onset, the patient could dimly discern movement in the right lower quadrants of the visual fields, and by March 28 the field defect was a left homonymous hemianopia with vision in the right half fields limited to appreciation of colors and large objects.

By April 19 vision in the right half fields was 6/12 with an absolute left homonymous hemianopia. At no time was visual agnosia, visual hallucinations, or denial of blindness encountered. Vomiting ceased after the first 24 hours, but headache persisted for some 10 days. The reflex and sensory signs could not be elicited 48 hours after admission to hospital.

A cerebrovascular lesion may result in hemianopia, which remains unrecognized by the patient. A second vascular lesion affecting the other hemisphere can, in such circumstances, result in bilateral visual loss. In the present instance, the patient was examined by an oculist shortly before the onset of this illness. The only defect found was a mild degree of hypermetropia. There is thus no evidence to suggest that he had a pre-existing embolic cardiovascular lesion, and that blindness resulted from further embolism to the other hemisphere. The sudden onset of visual loss suggested hysteria, an acute toxic or infective process, or a vascular lesion. The patient's mental attitude toward his symptoms, the associated headache and vomiting, and the absence of reflex blinking to menace did not favor a diagnosis of hysteria, and the later course of events excluded it. Toxic and infective processes were similarly ruled out. The dramatic onset, on the other hand, and the existence of a demonstrable source of an embolus strongly suggested a vascular lesion. The clinical picture was considered compatible with an embolus lodging at the bifurcation of the basilar artery and shedding secondary fragments in a symmetrical fashion to the calcarine branches of both posterior cerebral arteries.

Comment: The instances of the heart being the primary source of blindness from embolic arterial occlusion in either brain or eye are rare. True embolic occlusions of the central retinal artery have recently been reported after commissurotomy (Stassart and Lavergne, Am. J. Ophth., *47:* 90, 1959) and from an endocardial myxoma (Manschot, Am. J. Ophth., *47:* 385, 1959).

The dramatic case of cortical blindness in the patient discussed above is somewhat reminiscent of the equally dramatic report of cortical blindness from cardiac arrest by Hoyt and Walsh (A.M.A. Arch. Ophth., *60:* 1061, 1958). Hypoxia in the latter case was of necessity more diffuse and more profound than that following the occipital lobe infarction from an embolus riding at the bifurcation of the basilar artery described above.

Although also of cortical origin the blindness in the case described here was not associated with psychic visual symptoms such as spatial disorientation which makes the cortically blind often "blinder than the blind" to quote Hoyt and Walsh, perhaps due to ready, compensating vascular anastomoses.

The sequence of recovery, such as it was, followed a very similar pattern as illustrated by the visual fields of both cases.

BERTHA KLIEN

RUPTURED POSTERIOR FOSSA ANEURYSMS AND THEIR SURGICAL TREATMENT

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J. Neurol. Neurosurg. & Psychiat., 1959, *22:* 202

This paper gives a thorough and factual account of the present status of posterior fossa aneurysms. The use of vertebral angiography in the investigation of subarachnoid hemorrhage in recent years has enabled the presence of posterior fossa tumors to be detected during life. The clinical and radiologic localization of aneurysms at this site is now of importance, for with modern neurosurgical techniques, including hypothermia, these lesions are operable.

Twelve cases of subarachnoid hemorrhage due to posterior fossa aneurysms are described. The instance was the same in sex and age distribution as in supratentorial lesions. Clinical features of a characteristic of these aneurysms include weakness of the legs at the onset followed by nausea and vomiting, fluctuation in the level of consciousness, with stertorous breathing and fits. Cranial nerve signs consist of subhyaloid hemorrhages, contracted pupils, nystagmus, and 5th, 6th, 7th, and 8th nerve palsies. Transient hemiparesis occurs in the limbs, sometimes with bilateral pyramidal tract signs.

It is important to emphasize that both vertebral arteries may require injection to detect these aneurysms. The lesions are dangerous because bleeding usually recurs unless surgical treatment is undertaken. Of the 12 cases described by these authors, 6 were subjected to craniotomy, and 5 of these 6 patients made good recoveries. Hydrocephalus, however, may occur as a complication. Six additional cases were not subject to surgical intervention, only 1 made a satisfactory recovery, of the others, 4 died within 7 days after initial rupture, and a 6th died on the 26th day after rupture of the aneurysm. Of opthalmologic interest is the fact that in 1 patient visual failure due to subhyaloid hemorrhage reduced vision in one eye to counting fingers, and this never recovered due to secondary changes with the absorption of the hemorrhage in the macular area. Also of interest to ophthalmologists is the frequency with which signs other than intraocular hemorrhage were present, such as nystagmus and involvement of the extraocular muscles through cranial nerve palsies, particularly 6th nerve paresis. This contrasts with the typical 3rd nerve paralysis most commonly seen in carotid aneurysms or those involving the anterior part of the circle of Willis.

The principles of surgical treatment of aneurysms in the posterior fossa are similar to those which apply to the supratentorial aneurysms. Occlusion within the skull of the vertebral artery proximal to the ruptured sac after dilatation is an effective method of treatment, with the inherent danger here of production of an excessive fall of blood pressure which may lead to ischemia of the brainstem. In the 2 patients in which this occurred, however, good postoperative care resulted in recovery. The risk of thrombosis in the basilar artery pre-

viously given as a contraindication to surgery was not found in this small series of cases. Two methods of surgical approach are adopted. Aneurysms of the vertebral arteries and their branches are explored through a unilateral posterior fossa craniotomy, and even where the sac was found to be located far anteriorly in the fossa, relatively little difficulty in accessibility was experienced. Aneurysms of the basilar and superior cerebellar arteries were visualized by a supratentorial approach. This was carried out through a craniotomy flap exposing the posterior temporal and occipital regions. This area of the brain is then elevated and with an attempt to preserve the superior petrosal sinus, the tentorium is incised and on retracting the cerebellar hemispheres the basilar artery and its branches can be clearly seen with exposure of the 5th, 7th, and 8th cranial nerves. One disadvantage of this approach was that a homonymous hemianopsia invariably resulted, but it cleared up in 1 to 3 weeks. The principle that arteriography and operation should be performed as soon after the hemorrhage as the patient's condition permits was followed as far as possible.

Comment: The advent of newer surgical techniques, particularly hypothermia, has made surgical intervention in intracranial aneurysms a less hazardous procedure than in former years. Previous reports concerning posterior fossa aneurysms have emphasized the importance of these lesions, but at the same time have given a somewhat discouraging outlook as to their surgical approach. Since they are very likely to rebleed with a high mortality, it is apparent that not only should they be recognized early but vertebral arteriography, unilateral or bilateral, should be attempted at an early stage and neurosurgical intervention attempted.

THOMAS R. HEDGES

REFRACTION

OPTICAL AIDS FOR PERSONS WITH SUBNORMAL VISION

WILLIAM H. WYCKOFF AND HARVEY H. KALIL

New Orleans, Louisiana

South. M. J., 1959, *52:* 1461–1462

Congenital cataracts, which had been operated upon, microphthalmus, macular degeneration, and myopic chorioretinal degeneration seem to be the conditions most promising for optical aids. Diabetic re inopathy, retinitis pigmentosa, atrophy of the optic nerve and glaucoma offer the least promising results, since the field of view is reduced by every magnifying device. Visual aids are valueless if acuity is below 4/200 or counting of fingers at 2 meters. Visual impairment of

the conduction type responds better to a visual aid than do perceptive disorders. In small demarcated macular lesions, the spreading effect of magnification may give an acuity far better than anticipated.

Motivation is extremely important in the patient's acceptance of a visual aid. If visual acuity is 5/200 or better and without a constricted visual field, the patient is a good candidate for assistance. Often old people will not accept the strong reading corrections. Those with rigid reading habits have trouble in adjusting to a close reading distance. A compromise arrangement is possible in which a weaker reading addition is combined with a hand loupe.

For near vision, magnification of varying degrees can be obtained by use of several devices, loupes, high plus additions, telescopic units with plastic add caps, microscopic lenses, and an apparatus for projection enlargement. As magnification increases, reading distance and field are decreased. Magnification should be no greater than the predominant needs of the patient. Final tests should not be on a reading chart but on a telephone directory or the like. When a vocation demands reading a certain type of print, it is wise to tell the patient to bring this with him. An important point is a period of adequate training before the final prescription. It is often found that after repeated examinations, a lesser magnification is adequate than first supposed.

Loupes. An ordinary convex lens, the simplest type of magnifier, is widely used as a hand-reading glass or loupe. The field is limited not only by the diameter of the lens but also by marginal aberation.

Spectacle magnification. Ordinary spectacles fitted to give one or both eyes a closer focus is a simple magnifier. Magnification is obtained simply by reducing the reading distance. Binocular vision can be achieved with additions up to plus 8 to plus 10 D.

Microscopic lenses. The American Optical Company microscope lens is good and is available in powers up to times 10. Binocular vision may be obtained in the times 2 strength. The Volk conoid is superior to a plus 10 D. sphere because many partially sighted patients have nystagmus or eccentric fixation.

Telescopic aids. To use telescopic lenses, the patient must be stationary. Cheapest is a monocular appliance of 2-fold magnification that can be clipped over the spectacle lens of the better eye. The Kollmorgen appliance has units of 1.7 and 2.2 magnification. The Univis telescopic lens is inserted in the patient's distance correction at a position the bifocal segment usually occupies.

Bechtold and Feinbloom independently designed air-spaced compound-lens systems that give up to 14 to 20 magnification.

Projection enlargement. There are 2 types of projection enlargement: the Franklin Institute model enlarges 3 and 5 times and is good for vision at around 15/200; the megascope has been helpful in some cases of vision as low as 3/200.

Comment: The testing of patients with subnormal vision for visual aids would best be done as a continuation of the routine refraction. The publicity releases on low vision clinics have caused many patients to expect miracles. Some are bitterly disappointed

when they find they will not be able to drive a car, or walk through traffic unaided. Others should never have been referred, as they are too far gone, and are sadly let down.

The ideal situation would be for each practitioner to invest in the equipment necessary for evaluation of patients with subnormal vision in his own office. Such an investment would salvage more vision than many of the expensive and glamorous instruments we persuade ourselves to buy.

OWEN BELMONT

Basic Sciences

PHYSIOLOGY

THE DRIVER IN RELATION TO THE PHYSIOLOGICAL LIMITATIONS IMPOSED ON HIM AS A HUMAN BEING

F. S. Hansman

Sydney, Australia

M. J. Australia, 1959, *2:* 24–26

According to statistics, 85 per cent of accidents are due to human error, but little research has been done on the physiologic and psychologic factors causing human error in driving cars. I wish to present some well known factors from a rather fresh point of view.

The human brain cannot concentrate on one thing exclusively for more than an instant. On the one hand, any stimulus from the outside diverts attention, and on the other hand, if no stimuli come from outside the mind becomes drowsy. In driving we need a constant stream of light stimuli to keep us alert, but stimuli beyond a certain range are dangerous distractions.

Stimuli reach the brain from many sources, and those from any source may vary greatly. The mind becomes accustomed to constant stimulation of any sense organ if it is of unvaried intensity. The new super-highways approach a condition of monotony which tends to put drivers to sleep. The driver, in order to remain alert, requires variety in both the sources and the intensity of outside stimuli.

The eye is the most important sense organ. First, the eye must itself be capable of good vision, and second, the eye must have properly varied stimuli. Actually, on the road there are so many kinds of red lights for so many purposes that the driver can easily fail to note a red traffic light among the constant stimuli of other red lights.

The eye accommodates to changes of light up to a certain point, but sudden changes, especially as we grow older, can be confusing. Overly bright tail lights can be blinding, and those of varying intensity often suggest variations in distance, the dimmer ones appearing farther away than the bright ones. Intensity of rear car lights should be regulated with these facts in mind.

If the eye is focused straight ahead, it also sees objects within about 120 degrees, varying somewhat in individuals. In dense traffic or at high speed, the vision is largely concentrated straight ahead so that side-of-the-road signs may

not be noticed. A sign is not adequate if it is so placed that it is likely to be missed under existing driving conditions.

The mind intentionally selects certain stimuli from the great number in the environment, and gives them special attention. If, for example, the driver is concentrating on pedestrians, he may miss seeing something else. Traffic should be so arranged that the driver does not need to be aware of a multiplicity of visual stimuli at the same time. A driver going at 60 miles an hour is capable of registering about one object in each 88 feet.

Some research indicates that if auditory and visual stimuli reach the sense organs at the same time, the auditory stimuli are dominant. Auditory stimuli could be used to supplement visual stimuli. For example, radar impulses from certain signs could be picked up by instruments in the car, or auditory stimuli could be used to warn of changing lights or traffic signals.

Stimuli may be useful or they may be irritating, causing psychic trauma. Psychic trauma in driving is common. Static and structural causes, such as badly placed stop signs, poorly lighted streets, dangerous curves, should be eliminated.

The responses of the trained driver become automatic and are more efficient than those of a novice. There are also "driver habits" which are determined by the conscious mind and vary considerably among individuals. It would be advisable to establish good reflex responses before the driver gets on the road, and also to teach courteous driver habits.

Comment: This paper was read before an Institute of Transport in Sydney, Australia. Whether the author is a physician or not, I cannot know. He surely is not an ophthalmologist. The Medical Journal of Australia did well in publishing it. It has a new and refreshing point of view. It does not deal with better, bigger, and allegedly safer cars and bigger, better, and allegedly safer roads, but with the limitations of human beings, normal human beings, driving cars. The facts, of course, are not new. One need not be an expert in experimental psychology to know them. But the way the author has presented them is all his own. And he is very humane. Though he recognizes that the fault is mostly ours ("some 85% of road accidents are due to human errors"), he does not brand us guilty. "The driver who goes through a traffic light is fined . . . though he may be a most careful driver. Obviously the fault is not the driver's, but that of the authorities who allow lighting conditions to be such that the traffic light does not present at all times and under all conditions an adequate stimulus."

The most interesting of his statements bears repetition. "The fundamental requisite for concentration on driving is not only a constant stream of stimuli, but a constant variety . . . of these stimuli. . . . We have the paradoxical situation that in order to concentrate on driving, we have to have our attention continuously diverted from driving." And as to our supercars and superhighways? "It is obvious that the more closely we attain the 'ideal' motoring conditions, the closer we come to taking away from the driver the very stimuli which allow him to concentrate on driving."

The author certainly is on sound basis suggesting that warning signals, auditory in nature, would much add to alerting the driver all engrossed in visual clues.

For all his fine suggestions, we might forgive the author the following statement: "Accommodation has to deal with the ability of the eye to vary the amount of the pupil exposed."

ARTHUR LINKSZ

EXTRAOCULAR PROPRIOCEPTION

P. BACH-Y-RITA

Mexico, D. F.

Acta neurol. latinoamer., 1959, *5:* 17–39

This is a concentrated, 20-page review of 69 papers, and therefore its content can only be suggested in an abstract.

Proprioceptors with important functions in the regulation and control of movements have long been recognized in limb muscles, but, despite scattered earlier observations, were described in the eye with detailed observation only when Cooper and Daniel in 1949 reported on their study of muscle spindles in the extraocular muscles.

Muscle spindles are the chief stretch receptors, or proprioceptors, in muscles. Those in the eye muscles are similar to those in other muscles, but are much smaller and more delicate. They are, however, present in only the proximal and distal thirds of the eye muscles, but not in the middle third, which is especially rich in various types of nerve supply. Golgi tendon organs have also been found in eye muscles, as have several types of sensory organs.

Afferent fibers from the III, IV, and VI cranial nerves innervate the receptors, with which all eye muscles are richly provided. The nerve fibers vary from small, nonmyelinated fibers to large 14 μ fibers. Each muscle spindle is approached by a small nerve trunk, and the complex innervation and ramifacation of nerves within the muscle have been the subject of numerous studies. There is some disagreement as to the pathways by which impulses from the proprioceptors reach the brainstem, some investigators favoring the V and some the III nerve. Winkler's recent studies indicate that the proprioceptive impulses travel either in the oculomotor nerves or in the ophthalmic branch of the V nerve, or both. There is also some evidence that ganglion cells may be present in oculomotor nerves.

Despite intensive studies by many investigators, a number of which are reviewed, the mode of response of the receptors is still unclear. It is known that there is a very complicated pattern of excitory and inhibitory action involving interplay of impulses from muscle spindles, modulated by the efferent γ-system, and by impulses from tendon organs and other sensory organs. The function of the muscle spindles differs from that of other receptors in that the intrafusal fibers are innervated by small efferent "gamma" fibers which conduct at a rate of 20 to 40 meters a second in contrast to the large, ordinary motor fibers which conduct at "alpha" rates of 60 to 115 meters per second.

The γ-innervation apparently plays a role in making available the full range of dynamic sensitivity of the spindles. Cooper considers that γ-motor neurons are probably influenced by the retina and periorbital tissues, and Granit believes that the γ-system both improves the performance of the sense organ and serves to initiate movement and maintain tonus.

In studying central areas responding to stimulation of the receptors, it ap-

pears that at least some of the cell bodies of the proprioceptors of eye muscles are in the motor nuclei of the eye. While evidence is conflicting, the most recent physiologic studies suggest that the mesencephalic nucleus of the V cranial nerve is the central structure containing the largest number of cell bodies of eye-muscle proprioceptors. So far, projections to the cerebral and cerebellar cortex have not been determined.

While the existence of proprioceptors in the extraocular muscles is generally recognized today, there is some difference of opinion as to their importance. Since the muscle spindles are considered the chief organs of proprioception, the question arises as to why they are missing in some animals. Cooper believes that the main duty of the proprioceptors is to keep to co-ordinating centers of the brain stem and spinal cord informed about the muscles so that they are in a position to respond to lower reflexes or to the demands of voluntary movements. Probably such information is managed chiefly at subcortical levels.

Cooper believes that the proprioceptors also, in association with the retina, aid in controlling movements needed to fixate the eye. They probably play an important part in maintaining the eyeball in the optimal position for vision and in keeping the eyes ready to be moved as desired. Proprioceptors may also play a part in judging the distance of an object or the speed of a moving object. The movements of the eye in keeping the object in view are registered by the proprioceptors, which registration aids the central organs in judging speed and distance.

Comment: Reading of this review is a rewarding experience—and thanks are due to the author for having undertaken this labor. One would hardly believe without reading such a review that muscle spindles were discovered more than 100 years ago and that even their name is almost 100 years old. Ruffini (1893) was the first to assign sensory role to them. The work of Sherrington is, of course, classic and well known.

Muscle spindles in extraocular muscles were discovered and rediscovered several times, even in human extraocular muscles, and then usually forgotten, conveniently for those who, for theoretical reasons, believed that ocular muscular proprioception is not needed for vision (especially space perception), exasperating those who, for theoretical reasons, believed that vision (especially space perception) is unthinkable without ocular muscular proprioception. But now, finally, there is incontrovertible evidence that muscle spindles exist in human extraocular muscles, though not in the extraocular muscles of all species. This evidence was brought forth by Cooper and Daniel in 1949 (Brain, *72:* 1, 1949) and now even those who believe that proprioception is not needed for vision or the motor aspects of the mechanisms (fixation, for instance, or fusion) which subserve vision will concede that at least some mechanism for ocular muscular proprioception exists.

The same authors and their co-workers (see especially Cooper and Daniel, Quart. J. Exper. Physiol., *42:* 222, 1957) also brought evidence that different impulses do flow from extraocular muscles and that in the intact extraocular muscle, stretch causes a burst of impulses with a maximum rate of discharge at the peak of the stretch.

Then there are those mysterious γ-fibers. They are efferent and innervate, of all things, the muscle spindles causing, when stimulated, no contraction but an afferent discharge. Obviously we are dealing here with some kind of an upside-down reflex, an impulse with an efferent path to start with and an afferent burst as a response. Granit in his latest

book (*Receptors and Sensory Perception*, Yale University Press, New Haven, 1955) and Granit and Henatsch (J. Neurophysiol., *19:* 356, 1956) have given much thought to the working of this system. The trouble is that γ-fibers were found to be in abundant supply for the extrinsic ocular muscles of species which have muscle spindles and also of species in which no muscle spindles in extraocular muscles were yet demonstrated. Of course, there are other sensory apparatus in muscles besides spindles.

In spite of all the overwhelming evidence, there are still some unrelented who believe in the absence of proprioception in the extraocular muscles. Cogan (*Neurology of the Ocular Muscles*, Ed. 2, Thomas, Springfield, 1956) states that "one is aware of the position of one's eyes only by the knowledge that a certain amount of innervation has been supplied to turn the eyes and not by any stretch sense arising in the muscles themselves."

Of course, sensation and proprioception are two different things. This commentator in his book (*Vision*, Grune and Stratton, New York, 1952) has given an example from a different sensory modality taste. An afferent nerve fiber from the tongue might, by way of a reflex arc, initiate a process in an efferent fiber and cause salivation without this having any effect "higher up." No "sensation" need be involved. The sensation, the awareness of a taste, of, say, sourness or bitterness, is an entirely different matter which may or may not be initiated as the afferent impulse climbs over the centripetal rope.

Recently Breinin (A.M.A. Arch. Ophth., *57:* 176, 1957) emphasized that extraocular muscular proprioception also need not involve any awareness of the position of one's own eyes. The cybernetic influence of extraocular muscular proprioceptive mechanisms which, no doubt, exists is entirely independent of any awareness of position.

ARTHUR LINKSZ

A SCANNING PUPILLOMETER

L. S. KUMNICK

Am. J. Ophth., 1959, *48:* 259–261

"... the need for a completely automatic system for measuring, computing and storing the myriad of data gathered during the course of research has led to the development of the electronic pupillometer." A "working model" of the infrared scanning system of this instrument has been built. This device furnishes a graphic record of the pupillary movements, evidently of one eye only. Apparently, an ink-writing recorder is used, and it is stated that the responses may also be recorded on magnetic tape. The scanner is able to ... "produce faithful records of pupil diameter ... with an accuracy of ±0.1 mm ... [and] ... dynamic response over a range of zero to two cycles per second (limited by recorder), otherwise, zero to eight cps...." A light stimulator with adjustable stimulus intensity, duration and intervals is included in the equipment, but it is not stated what light source is used.

Work on additional circuits for automatic processing of experimental data is promised for the future. "... the apparatus planned represents such a funda-

mental departure from the present methods of pupillography that it should make it a practical source of important information, not now available, for many medical specialties and disciplines and for experimental studies, as well as for the studies planned for this project. New lines of investigation may be opened and new hypotheses developed which may be tested."

Experimental work on the effect of light stimuli of different intensity and time characteristics, on "hippus", macular diseases and demyelinating diseases are reported to be in progress or in the planning stage. This work will ". . . yield valuable results for planning future experimental designs."

Comment: This report claims a great deal of accomplishment without giving a single pertinent fact. The scanning system is not described. When told that it is capable of "producing faithful recordings of pupillary responses. . .with an accuracy of ±0.1 mm," we would, of course, be interested in a definition of this accuracy. Does the statement refer to long-term stability, to linearity, to histeresis, to the ability to follow small pupillary changes, or does the *combined* error of stability, linearity, etc. add up to 0.1 mm.? How is the accuracy determined, and what range of eye movements is allowed without exceeding the stated error? A "special discriminator system" is mentioned but nothing is said about its principle or about how it is "properly set" so that "the point of optimum adjustment has been achieved. . .to. . .accommodate a wide range of absorption ratios." "Precision focusing and positioning of the optical system to within 0.001 inch" is said to be accomplished, but it is not stated by what means, or how accurate positioning of the patient's eye is maintained throughout the experiment, presumably in a dark room. A description of the "unique system for insuring stability of the head position. . .thus affording the subject a high degree of comfort" would certainly have been welcome, while a method for fixation of the patient's gaze is not even mentioned. Nothing, likewise, is said about the source of the infrared energy used in the system. It would be important to know the wavelength of this light and the method by which it is prevented from heating the patient's eye. The meaning of the expression "dynamic response over a range of zero to two cycles per second" is not clear. If it refers to an ability of the system to detect reversals in the direction of the movement at the rate of 2 per second, it would be too slow, because the normal iris is able to move with discrete oscillations at a rate of 3.6 to 4 per second.

The author was a guest in our laboratory at a time when construction plans for an electronic scanning pupillograph were drawn up (1950–1952). During this time, the requirements and the possible errors of such systems were amply discussed. She therefore ought to be aware that the merit—or the complete worthlessness—of such instruments hinges on the technical details mentioned above. She should also know that one-channel recording of the pupillary reactions is not acceptable in clinical pupillography. The diagnostic system of pupillography, which I developed during the past 35 years, is based on the analysis of pupillary movements, with the aim of determining the normal reflex pattern and distinguishing the various pathologic deviations from this pattern. The reactions of the right and the left eye should be recorded simultaneously because small lesions which do not cause a marked change in the pupillary reflexes are often unilateral or asymmetric; they can be detected only by the slight differences in the reactions of the two eyes. Much of the delicacy of the method will therefore be lost when the movements of one pupil only are recorded. It is less important to collect and "store" "myriads of data" than to have physiologically and clinically pertinent facts recorded as completely as possible. In the majority of patients, accurate records of the responses of the two pupils

to a limited number of stimuli suffice for the establishment of a clinical diagnosis. In contrast, one-channel recording which does not allow an analysis of the different types of anisocoria is not only worthless but frequently misleading for the clinician and therefore dangerous for the patient. It is, at best, of limited value in some fields of research.

Coming from this particular author, the claim of novelty is surprising. The two-channel electronic Pupillograph which was planned in our laboratory in 1950 has been completed some years ago* and has been in constant use, both clinically and for research experiments, for more than 3 years.[1-5] The author fails to describe a single improvement of the technique, while the part of her instrument which would"...represent such a fundamental departure from the present methods of pupillography that it should make it a practical source for important information, not now available, for many medical specialties and disciplines..." is merely a "future plan."

Finally, the author's claim that the effects of variations of stimulus intensity, duration and frequency have not been studied, especially not the redilation phase after contractions to light, conflicts with the facts contained in the voluminous literature on these subjects.[6]

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Otto Lowenstein

* The instrument was constructed by the General Precision Laboratory, Inc., of Pleasantville, N. Y., with our cooperation. It has been found to give reliable performance under clinical conditions. A general description of the method and definition of the accuracy achieved is contained in publication,[1] while the electronic and other construction details are described in publication.[5]

A NEW CONCEPT OF THE SYMPATHETIC PATHWAYS TO THE EYE

A New Technique to Avoid a Horner's Syndrome

L. T. Palumbo

Surgery, 1957, *42:* 740–748

Sympathetic denervation is done in a number of clinical syndromes. According to the author, upper dorsal sympathectomy is valuable in the following conditions:

Angina pectoris
Peripheral arteriosclerosis
Raynaud's disease
Buerger's disease
Causalgia
Frostbite
Shoulder-hand syndrome
Paroxysmal tachycardia
Thrombosis of major vessels
Arteriovenous fistula and aneurysm
Coronary heart disease
Acrocyanosis
Scleroderma
Sudeck's atrophy
Chilblains
Hyperhidrosis
Carotid sinus syndrome
Phantom limb
Erythromegalia

The various surgical techniques for sympathetic denervation of the upper extremities, head, neck or heart and coronary vessels left much to be desired because of the indirect and difficult surgical approach. Since 1953, the author employed a new surgical approach to the upper sympathetic chain, consisting of an anterior, transthoracic, transpleural incision through the third intercostal space. This approach gives the surgeon ample room under direct visualization of the anatomical structures, which permits faster, more meticulous dissection than was possible with the older methods.

On the basis of his experience, the author disputes the commonly accepted opinion on the path of the sympathetic pupillodilator fibers from the spinal cord to the cervical sympathetic chain.

According to currently accepted theory, the sympathetic fibers take their origin from cell bodies in Budge's ciliospinal center in the cervicothoracic spinal cord (C8-T2). The sympathetic fibers leave the spinal cord mainly in the first and second thoracic ventral roots and, via the rami communicantes, enter the sympathetic chain at the level of the first thoracic sympathetic ganglion, *i.e.*, the inferior portion of the stellate ganglion, as the stellate ganglion includes the fused first thoracic and inferior cervical ganglia. The pupillodilator fibers then turn cephalad, traveling via the inferior cervical ganglion (upper part of the stellate ganglion), the subclavian ansa of Vieussens and the middle cervical ganglion to the superior cervical ganglion, where they synapse with the postganglionic sympathetic neurones.

According to the author's results, the sympathetic fibers, after leaving the spinal cord with the ventral roots C8-T2, fail to enter the rami communicantes and do not traverse the first thoracic sympathetic ganglion. Instead, they enter the sympathetic chain by a separate paravertebral route at the level of the inferior cervical, *i.e.*, the upper portion of the stellate ganglion. In 45 patients in whom the rami communicantes from the first and second thoracic segments and the first thoracic sympathetic ganglion (lower ⅓ of the stellate) were divided and resected, miosis and ptosis did not develop, even though anhydrosis in the face and neck was complete. In 2 patients in whom the upper portion of the stellate ganglion was removed or damaged by manipulation, the sympathetic innervation of the eye was destroyed. In a third case, Horner's syndrome developed bilaterally in two successive operations without undue trauma to the inferior cervical ganglion. This case was regarded as a variant in the course of the sympathetic fibers.

Contrary to the commonly held opinion, it is thus possible to avoid the ptosis

and miosis of Horner's syndrome in upper thoracic sympathectomy, even when the first and second rami communicantes are cut, as long as the inferior cervical ganglion (upper part of the stellate ganglion) and its connections to the spinal cord are left intact.

Comment: This interesting paper confirms for man findings like those of Langley[1, 2] who showed that in the cat, the sympthetic fibers for pupillary dilation and the extra-orbital smooth muscles leave the spinal cord from higher segments (C8-T2) than the fibers for vasoconstriction (T2-T5), heart acceleration (T1-T5), piloerection in the face and neck (T4-T7) or sweat glands in the anterior extremities (T5-T9).

The new operation spares the patient the complication of a Horner's syndrome, while it yet accomplishes the desired neurovascular effect. Since earlier operations in man were done by a less direct and therefore necessarily less accurate method, the results concerning the nervous pathway for pupillary dilation *in man* appear conclusive. The results are not necessarily applicable to animals. The author's peculiar reference to the "pupillociliary pathways" and his mistaken opinion that the ciliary muscles accomplish pupillary dilatation, do not detract from the value of his findings.

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Otto Lowenstein

MICROBIOLOGY

AUTO-IMMUNITY AS A CAUSE OF DISEASE

Editorial

Brit. M. J., 1959, Oct., 747–748

One of the most important observations of the early immunologists was the failure of animals to produce auto-antibodies—that is, antibodies to their own antigens. The first half of the twentieth century contributed little to our understanding of this, and to many students it appeared to be a fundamental and inviolable law of nature. But research into the production of antibody[1] suggested that the body's cells must contain some apparatus to form antibodies which enables the distinction to be drawn between "self" and "not self," and it is presumably the existence of this apparatus that is responsible for the usual failure to form auto-antibodies. Once the existence of such an apparatus is admitted, the possibility of its breakdown must be considered, and indeed the

fact of auto-immune disease is now unquestionably established. Its extent and importance, moreover, though at present largely conjectural, are likely to be considerable.

In his Croonian Lectures, reproduced in this and last week's issues of the *Journal*, Sir Macfarlane Burnet draws attention to the inadequacy of classical immunological theory to account for the production of auto-antibodies, and further develops his theory of clonal selection of antibody-producing cells in which auto-antigens have a central role. In contrast to the classical "template" theory, Burnet's concept allows antigen no part in determining specificity of antibody. Instead, he envisages antigen as either stimulating or inhibiting the activity of cells whose immunologically specific products or properties are already genetically determined.

In the absence of precise knowledge of the mechanism by which antigen stimulates the production of antibody, it is well to remember that modification of antigen, as well as of cell clones, may lead to production of auto-antibody. A study of several examples of auto-immune disease throws light on this problem. Thus J. F. Ackroyd's work on purpura caused by apronal ("sedormid")[2] has shown that at least in some cases the combination of a foreign non-antigenic substance or hapten with an endogenous protein may sufficiently modify the latter to render it antigenic. As a consequence, antibodies are formed to the complex, which in this example consists of platelet and apronal. The resultant clumping leads to thrombocytopenia and haemorrhage. The converse, in which the endogenous factor is the hapten and the exogenous factor the protein, has been suggested as the method underlying the relationship between streptococci and such diseases as rheumatic fever and glomerulonephritis.[3] The ease with which non-antigenic substances such as polysaccharides may be converted to full antigenicity by streptococci lends some credence to this hypothesis.[4]

The work of P. B. Medawar and his colleagues[5] on what is usually called specific immune tolerance would illustrate very well Burnet's concept of the "forbidden clone." They have shown that the reactivity of the antibody-forming tissues is largely determined by the antigens present when these tissues are reaching maturity, and in consequence tolerance to a specific antigen can be induced by injecting it some time before production of antibody begins. This varies from species to species but is usually about the time of birth. Presumably tolerance is never acquired to such antigens in the body as lack access to the antibody-forming tissues, and the readiness with which antibodies to thyroglobulin are produced in man may be explicable in this way. Finally, and this may well prove to be the most important of all, auto-antibodies could perhaps arise as a result of some change in the antibody-forming cells themselves, possibly by somatic mutation. In consequence, tolerance might be lost to one or more of the readily available antigens, especially if the postulated homoeostatic mechanism due to inhibition by antigen is also impaired. The auto-antibodies to red-cell antigens found in certain cases of haemolytic anaemia may be due to such a change.

The concept that disease can arise as a consequence of an immune reaction

directed against one or more of the antigenic constituents of an individual's own tissues has received considerable support from the results of animal experiments. Lesions in many ways resembling those occurring naturally in man have now been successfully produced in the laboratory in an impressive variety of organs, including the brain,[6] spinal cord and peripheral nerves,[7] the thyroid[8, 9] and adrenal glands,[10] the testes,[11] and the kidney.[12] In almost all these experiments use has been made of the adjuvant effect of acid-fast bacilli or of fractions obtained from them. How these adjuvants act to overcome the usual resistance to the development of auto-immune reactions is a major problem perhaps one of the most urgent problems in this field awaiting solution.

Of the many diseases suspected of arising as a result of auto-immune reactions the evidence is most convincing in the acquired haemolytic anaemias, Hashimoto's disease,[13] and certain cases of male infertility associated with circulating antibodies to spermatozoa.[14] The evidence for a similar pathogenesis of the collagen diseases is less well founded, though in both rheumatoid arthritis and systemic lupus erythematosus serum factors are present which have many of the properties of antibodies against various body antigens—for example, denatured gamma globulin in rheumatoid arthritis[15] and various components of cell nuclei and cytoplasm in S.L.E.[16] But the lack of correlation between the clinical state and the level of these antibodies, both in the natural and experimentally induced diseases, and the failure to enhance the symptoms in any of these conditions by passive transfer of antibodies, have led to the view that they are merely interesting by-products of the disease process. Nevertheless, the discovery of these antibodies in most patients with rheumatoid arthritis and systemic lupus erythematosus has provided a tremendous stimulus to the search for further evidence of auto-immunity as a cause of disease, and it may well be that, as with the tuberculin reaction and other manifestations of delayed hypersensitivity, the active agent is not to be found in the plasma proteins but in the fixed and circulating cells of the lympho-reticular system.

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Comment: The possible relationship of auto-allergic uveitis to other types of endogenous uveitis is still speculative; this is the feeling of Waxman and also of Kimura with which this reviewer agrees. Nevertheless, as Kimura has pointed out, this is an interesting approach to the study of uveitis and warrants a great deal more work utilizing all the newer techniques of immunology.

IRVING H. LEOPOLD

PROWAZEK'S BODIES IN TRACHOMA AND THEIR EPIDEMIOLOGICAL SIGNIFICANCE

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Vestnik. oftal., 1956, *69:* 3–9

Recent investigations have almost completely confirmed the virus origin of trachoma. The Prowazek-Halberstaedter inclusion bodies are considered to be the only causal agents of this infectious disease. The present study, in which conjunctival scrapings were examined for Prowazek-Halberstaedter bodies, was undertaken to determine whether, in foci of trachoma, a carrier state exists in clinically healthy persons and in those who are clinically cured, that is, in Stage IV (convalescent).

For the purposes of this study, the Prowazek bodies were classified as typical or atypical. Bodies with definite granulation in the form of caps around the nucleus of the epithelial cell were regarded as typical. Those in which the granulation existed in the form of compact granular clumps disposed near the nucleus of the cell, or those that were found in a stage of lysis, were considered atypical. The scrapings studied were obtained from 2933 persons, 1297 of whom were clinically healthy. Of the remaining 1636 persons, 53 were suspected of having trachoma; 13 had Stage I trachoma; 19 were in Stage II, 491 in Stage III, and 795 in Stage IV of trachoma; in addition, 151 persons had catarrhal conjunctivitis, subacute and chronic, and 114 had follicular conjunctivitis. There were 1297 clinically healthy persons. On examination of the scrapings, Prowazek bodies were found in 3.8 per cent of the persons in whom trachoma was suspected. In patients who had trachoma, they were found in the following proportions: Stage I, 23 per cent; Stage II, 10.5 per cent; Stage III, 9.49 per cent; and Stage IV, 4 per cent. They were found in 0.7 per cent of the patients with catarrhal conjunctivitis, in 1.8 per cent of those with follicular conjunctivitis, and in 1 per cent of those who were clinically healthy. If the atypical Prowazek bodies found are also taken into account, the percentage of positive results is increased in all patients except those suspected of having trachoma and those with Stage I trachoma. The percentage of atypical bodies as compared with typical ones

was particularly high in clinically healthy persons (typical, 1 per cent; atypical, 1.85 per cent; together, 2.9 per cent).

Remaining elements of unhealed trachoma in the form of small focal infiltrations and solitary follicles deeply situated in the tarsal conjunctiva or at the corners of the cartilages (Stage III) were found in almost half of the patients in whom the existence of Stage IV trachoma had been established by ordinary methods of investigation. Prowazek bodies were found even in those in whom, the diagnosis of healed trachoma had been established biomicroscopically, *i.e.*, they were convalescent carriers, a fact of epidemiologic significance. Moreover, in foci of trachoma, the possibility that the disease may be carried by persons who are clinically completely healthy has not been excluded. Similarly, patients with the so-called *forme fruste* of trachoma, latent trachoma, and microtrachoma are often recorded as healthy on ordinary examination but are in fact virus carriers.

The criterion of the state of authentic cure in patients with trachoma, that is, one which provides complete safety for those around the patient, with a guarantee against relapses, has not yet been established; consequently, at the present stage of the fight against trachoma, registration of healed (Stage IV) cases and their constant observation for an unlimited period of time are obligatory. Antirelapse therapy to prevent reactivation of the virus is desirable, and relapses, when they occur, should be treated at once.

Comment: The author raises a number of interesting questions regarding latency in trachoma, the difficulty of defining the healed state of the disease, and the possibility of a carrier state. Since cultivation of the virus has been attained, there is no longer any doubt about the role of the Halberstaedter-Prowazek inclusion body in the disease. Nevertheless, considerable difficulty is sometimes encountered by technicians, clinical pathologists, and ophthalmologists not wholly familiar with the psittacosis group of viruses in their efforts to distinguish true inclusions from pseudoinclusions due to pigment granules, nuclear extrusions, engulfed cellular debris, etc. As a result, considerable caution must be used in interpreting claims of the demonstration of these bodies in conditions other than active trachoma or inclusion conjunctivitis. For example, Bodian's claim that he found inclusions in normal eyes in natives of the Fiji Islands was based on the confusion of cytoplasmic melanin granules with virus bodies.

In many thousands of specimens examined I never have been able to find the Prowazek bodies in conditions other than trachoma and inclusion conjunctivitis. It should be pointed out, moreover, that although trachoma without subjective symptoms can exist, particularly in children, it has always been possible with the biomicroscope to detect both the conjunctival and the corneal changes of the disease in these subclinical cases. Mention should be made of the value of the cortisone provocative test in Stage IV trachoma: a microscopic and clinical exacerbation should occur in insufficiently treated cases.

P. THYGESON

Dr. Ernst Fuchs

Classics of Ophthalmology
JAMES E. LEBENSOHN, Editor

IRIDO-CYCLITIC SYMPATHICA

ERNST FUCHS, M. D.

Vienna

Text-Book of Ophthalmology, 12th German Edition, translated by Alexander Duane, M. D., New York, N.Y., J. B. Lippincott Co., Philadelphia, 1923, pp. 682–685.

When an eye is affected with irido-cyclitis in consequence of an injury, either symptoms of irritation or else an actual inflammation may develop in the other eye.

Sympathetic irritation (irritatio sympathica) consists in photophobia, lacrimation, or actual pain. Sometimes also weakness of accommodation is present, so that when the patient tries to do fine work the vision gets indistinct and the work has to be given up. Such symptoms, however, are to be called by the name of sympathetic irritation only when objective signs of inflammation are absent, for when once these make their appearance, it is a question, not of sympathetic irritation, but of sympathetic inflammation. A characteristic sign, furthermore, of sympathetic irritation is that it disappears at once and forever when the primarily affected eye is removed.

Sympathetic inflammation (ophthalmia sympathica) consists in the development of an irido-cyclitis in the second eye. The eye primarily affected is called the "exciting eye," that which is affected secondarily the "sympathizing eye." Sympathetic inflammation develops sometimes in immediate conjunction with preceding symptoms of sympathetic irritation, sometimes without any intermediary symptoms at all and quite unforeseen.

The beginning is often insidious. In conjunction with an insignificant reddening of the eye, deposits—which are never wanting in the beginning of a sympathetic ophthalmia—appear upon the cornea. Then a few posterior synechiae and fine opacities in the vitreous develop, and the ophthalmoscope shows hyperaemia of the retina and optic nerve. In favorable cases the disease reaches no higher pitch and at length gets well, leaving either no trace of its presence or a few posterior synechiae. Unfortunately such mild cases are the exception. The rule is that the symptoms of inflammation slowly or quickly increase; more and more adhesions of the iris develop, and the visual power becomes more and more reduced. Hypopyon, however, ordinarily does not occur even when the inflammation is severe. Although sometimes intervals in the inflammation with some

improvement in sight occur, yet these are not lasting, and finally, owing to the constantly recurring inflammation, there ensues in spite of all treatment the formation of a pupillary membrane and of an annular or total posterior synechia. Then, in consequence of the seclusion of the pupil, increase of tension may set in, but this is commonly not of long duration, since cyclitic membranes have also formed in the vitreous, and by their shrinkage the intra-ocular pressure is once more lowered and finally atrophy of the eyeball is produced. As a rule, therefore, the sympathizing eye is lost.

In view of the great gravity of sympathetic ophthalmia, it is important to know its early danger signs, *i.e.*, those that occur before the stage of actual exudation. According to Brownlie, these are a contraction of the visual field, a spindle-shaped enlargement (elongation of the vertical diameter) of the blind spot, congestion of the optic disc and retinal vessels, loss of visual acuity, paresis of accommodation, and changes in the blood count (marked increase in the large uninuclear leucocytes, some increase in the lymphocytes, decrease in the polymorphonuclear cells). According to Gifford, however, the blood changes, although well-marked in sympathetic ophthalmia, are not pathognomonic since they are found frequently in chronic uveitis and like conditions.

It is supposed that the sympathetic disease may appear not only in the form of an irido-cyclitis, but also under some other guise. The greatest variety of affections have been described as sympathetic. Among non-inflammatory affections, cases of paralysis of accommodation, of amblyopia, and of blepharospasm have been adduced as sympathetic; among inflammatory affections in the posterior division of the eye, neuritis, chorioiditis, and glaucoma; and in the anterior division of the eye, conjunctivitis and keratitis. However, the only conditions in which the connection has been surely proved are sympathetic neuritis and chorioiditis. The former occurs very rarely and gives a comparatively good prognosis. As regards the chorioiditis, this probably is present in all severe cases, of sympathetic irido-cyclitis, but cannot be diagnosticated, because the cloudiness of the media prevents ophthalmoscopic examination. Hence we get the ophthalmoscopic picture of chorioiditis only in those comparatively mild cases, in which the anterior segment of the uvea is affected but little or not at all; and such cases are rare. Sympathetic chorioiditis is marked by the presence of numerous small yellow patches which occupy especially the periphery of the fundus. In other cases observers have often gone too far in taking the sympathetic nature of the disease for granted. The fact that an eye has been destroyed through traumatism by no means justifies us in regarding, without further proof, any subsequent disease of the other eye as sympathetic. This assumption should be made only when such disease presents the characteristic clinical picture of sympathetic irido-cyclitis, or when, upon the enucleation of the eye first diseased, the symptoms in the second eye recede too rapidly to be accounted for upon any other assumption than that the affection of the second eye was caused by that of the first. The converse of this inference does not hold good—that is, the fact that enucleation of the first eye does not influence the course of the disease in the second is no argument against the sympathetic nature of the

lesion; indeed, it is a well-established fact that when sympathetic ophthalmia has once broken out, enucleation of the eye first diseased is not generally able to cause much change.

The affection of the *exciting* eye, which gives rise to a sympathetic inflammation, is always an irido-cyclitis, and is, in fact, almost without exception, an irido-cyclitis traumatica, due to a penetrating injury. In this category, of course, are to be reckoned the operations that are attended with opening of the eyeball, in case they are followed by inflammation.

As a matter of prognosis and treatment, it is important to know that, in spite of there being a violent inflammation of the primarily diseased eye, sympathetic ophthalmia occurs very rarely in (1) suppuration of the cornea (in ulcus serpens, after acute blennorrhoea, etc.) and in its sequelae, phthisis corneae or staphyloma of the cornea, and in (2) panophthalmitis and the phthisis bulbi that follows it; and it never occurs in (3) absolute glaucoma.

The *point of time* at which the greatest danger of the transmission of the inflammation exists is when the irido-cyclitis in the injured eye is at its height. Hence sympathetic inflammation makes its appearance, in most cases, from four to eight weeks after the injury to the first eye has taken place. (It may occur as early as four days after the injury—Cahillous cited by DeLapersonne). Later than this, when the traumatic irido-cyclitis has subsided and the eye has fallen a prey to atrophy, there need be generally no fear of sympathetic inflammation, so long as the atrophic eye is free from inflammation and is not painful, either spontaneously or to the touch. The danger for the other eye does not develop again until the atrophic eye becomes once more the seat of inflammation and of pain—an event which, to be sure, very frequently occurs. In this way an eye which has been carried for many years in an atrophic state without causing trouble may suddenly become the cause of a sympathetic inflammation. While, therefore, the minimum period for the development of sympathetic irido-cyclitis is but a few days, no limits can be set to the maximum period; sympathetic inflammation has been seen to appear forty years and more after the injury of the first eye. An eye which has been destroyed in consequence of injury is therefore a constant source of danger to the other eye.

To excite sympathetic inflammation it is not necessary for the injured eye to be perfectly blind. Cases occur in which the eye has retained a remnant of visual power after the injury and the irido-cyclitis following it, and has yet given rise to sympathetic inflammation. In that case it may happen that the sympathetically affected eye undergoes complete destruction, while the injured eye is still used to see with.

Can an irido-cyclitis of *non-traumatic origin* be transmitted to the other eye? We very often see irido-cyclitis develop spontaneously first in one eye, then in the other. But we must not therefore at once conclude that the inflammation has been transmitted from one eye to the other. It may be that we have to do with a deeply seated common cause, generally of constitutional nature, which makes itself felt first in one eye, then in the other. We should therefore regard an irido-cyclitis occurring in the fellow eye as sympathetic, only in case the

inflammation in the first eye is certainly a purely local one and not dependent on constitutional causes. This is true of two varieties besides the traumatic, *i.e.*, of the irido-cyclitis which sometimes occurs after the perforation of a corneal ulcer, and of that which develops in eyes with an intra-ocular tumor. If the latter becomes necrotic, a violent inflammation of the inner coats of the eye results. In these two cases a genuine sympathetic inflammation of the second eye is observed, even though it is rare.

The way in which the inflammation is *transmitted* from one eye to the other is as yet unknown. Not every severe traumatic inflammation of the eye leads to sympathetic disease of the other; whether this develops or not depends upon two conditions:

1. Upon the character of the inflammation of the injured eye. To a certain extent this has been known for a long time; thus we are aware that in cases in which the injury produces ulcus serpens or panophthalmitis, sympathetic inflammation usually does not set in. To excite this an irido-cyclitis is required. But again it is not every traumatic irido-cyclitis, even when destructive, that causes sympathetic inflammation, but only an irido-cyclitis of a quite well defined sort, which is marked by a peculiar, very characteristic anatomical condition. Unfortunately, we have not as yet advanced so far as to be able to conclude from the clinical picture itself whether in a given case we are dealing with this particular sort of irido-cyclitis.

2. If now this particular kind of irido-cyclitis does really develop after an injury, a possibility is then afforded that this inflammation may pass to the other eye, but such passage does not necessarily follow. For it to occur, a series of conditions must be involved, affecting the paths by which the passage takes place. What these conditions and indeed what the actual paths are we do not know. By some the transmission has been thought to take place by the ciliary nerves. But since the ciliary nerves of the two sides are nowhere in direct connection, the transmission in this case could be effected not by direct migration, but only in a reflex way. As a matter of fact it is scarcely to be doubted that sympathetic irritation is effected by way of the ciliary nerves. In fact even in slight changes occurring in one eye (for example, a foreign body in the cornea) we observe lacrimation and photophobia in the other. But that an actual inflammation with serious anatomical changes should develop in a reflex way is, in our present state of knowledge, inadmissible. Hence others, including Mackenzie, who first taught us to know sympathetic ophthalmia, have regarded the optic nerves as the medium by which bacteria or toxins are transmitted from one eye to the other. But this hypothesis is opposed by the fact that sympathetic ophthalmia does not actually begin in the optic nerve and when changes are found in the latter these decrease instead of increasing as we go backward. Furthermore, the optic nerve of the exciting eye may be completely divided and yet sympathetic ophthalmia may develop. Hence the view has prevailed that the transmission of bacteria or other agents exciting the inflammation takes place through the blood (Berlin). It has been suggested that bacteria by prolonged lodgement in the exciting eye may acquire a special affinity for the uvea

so that when finally let loose in the circulation they start up a peculiar inflammation in the uvea of the other eye but affect no other organ (Gifford, O'Connor).

Another view is that sympathetic inflammation is an anaphylactic disease. In this view the transmission of bacteria or of disintegrated uveal tissue from the affected eye so sensitizes the other that the latter falls a prey to infection from other sources (especially to focal infection from the teeth, tonsils etc). There are a number of arguments in favor of this view, but it cannot yet be regarded as proved.

Investigation of this subject has been frustrated by the fact that we have been able in no way to demonstrate the presence of the bacteria that are supposed to excite the sympathetic inflammation. Furthermore we have had no opportunities for examining a sympathizing eye in the first stages of the disease, nor is experimentation on animals of any help to us either. Not only does sympathetic ophthalmia fail to occur spontaneously in animals, but the attempt to produce in animals an undoubted sympathetic inflammation experimentally has also failed of success.

Brownlie and others have pointed out the analogy that sympathetic ophthalmia shows in various ways to the protozoal diseases (syphilis, malaria, trypanosomiasis). This analogy is somewhat supported by the fact that salvarsan exerts a favorable effect on the disease.

Changes in Sympathetic Inflammation.—This infiltration has been especially studied in the exciting eye (that is the one which was injured and is the first affected). Here, in addition to the evidences of an ordinary plastic irido-cyclitis, such as cyclitic membranes with detachment of the retina, we find the uvea distended with densely crowded lymphocytes and plasma cells. In most cases there lie in the midst of this uniform infiltration focal collections of large (epithelioid) cells, which not infrequently have giant cells between them. Nodules are thus produced which often are like tuberculous nodules. This peculiar infiltration often is present in only a few spots, so that isolated nodules are seen here and there in the iris, ciliary body, or chorioid. In other cases the uvea is occupied by them either largely or wholly and thus often becomes extremely thickened so as to fill, more or less completely, the interior of the eye. Sometimes the infiltration even makes its way into the sclera, which is permeated with scattered nodules, and in this way perforation of the sclera and extra-ocular proliferation may result.

Up to the present time it has not been possible to demonstrate the presence of bacteria in the nodules. Nevertheless there is scarcely a doubt but that here too we are dealing with an affection produced by bacteria, which, however, do not cause acute suppuration but, after the analogy of many other bacteria (for instance the tubercle bacilli), cause chronic proliferations. This inflammation has the property of being transmissible to the other eye. Of the sympathizing, that is the secondarily affected eyes, only a few have so far been got for examination, but then generally the same peculiar changes have been found.

Treatment.—If we wait to perform enucleation until the first signs of sympathetic disease show themselves, we are generally too late. Hence, to advise

enucleation at the right moment is one of the most important tasks that the physician has to perform. To do this properly we must bear in mind the fact that the danger of sympathetic inflammation, is almost confined to the traumatic cases. If it is a case of recent inflammation, enucleation is indicated as soon as we see that blinding of the injured eye is inevitable. We recognize that this is the case by the increasing deficiency in the perception of light (this especially in the plastic cases; in purulent conditions, this not always an absolute guide). If the traumatic inflammation has already run its course, and a greater or less degree of atrophy of the eyeball has supervened, enucleation is still indicated if the eye is sensitive to pressure or if it gets inflamed often. It is only when the eyeball is entirely and permanently free from irritation that the demand for enucleation is not imperative. But the patient ought to be warned that he should report immediately for enucleation, if pain or inflammation happens to set in anew, and should be kept under periodic observation so that we can detect at once any evidences of inflammation or any of the danger signs of sympathetic disease.

When sympathetic ophthalmia has already broken out, the effect of enucleation is uncertain. In the lighter cases it appears to exert a favorable influence upon the course of the sympathetic inflammation; in severe cases, on the contrary, it is often of no avail.

Although enucleation generally affords a sure safeguard against sympathetic inflammation of the other eye, nevertheless a series of cases is known in which in spite of enucleation, inflammation has subsequently made its appearance. In every instance, it has set in within a short time—from a few days to a few weeks—after the enucleation. The longest interval so far observed is fifty-three days (in a case of Stephenson's cited by DeSchweinitz). Yet even when this does happen, enucleation does not fail to exert a favorable effect, since in the great majority of these cases the sympathetic inflammation runs an unusually favorable course, probably because the removal of the first eye prevents the constant emission from it of new impulses for the production of inflammation.

Operations in a case of sympathetic ophthalmia generally give a bad result, since they start up the inflammation again, so that the newly formed pupil is once more closed by fresh exudate. Hence operations are done only when it is absolutely requisite (*e.g.*, when done on account of increase of tension); other operations, such as, for example, an iridectomy for optical purposes, are put off as long as possible, preferably for years.

Editorial comment. In a histologic study of 200 eyes Fuchs was able by the pathologic evidence alone and without reference to the case history to separate accurately the 35 eyes which had excited sympathetic ophthalmia. Though an additional 16 eyes were found to have induced in a fellow healthy eye symptoms of photophobia, lacrimation, blepharospasm, pain, fatigue or paresis of accommodation, Fuchs proved that this syndrome of sympathetic irritation was simply reflex as the excised eyes showed none of the signs characteristic of sympathetic inflammation. His studies indicated no special age predilection, as he found that the incidence of sympathetic disease corresponded fairly well with the age distribution of the general population. Among the pathologic features of

the disease Fuchs noted nodules of pigment cells undergoing depigmentation (Dalén-Fuchs nodules) which corresponded to the small drusen-like white spots seen ophthalmoscopically (Dalén's spots). The evidence suggests infection as the cause of sympathetic ophthalmia and a virus as the probable offending organism. Allergy to uveal pigment may be a factor in certain manifestations of the disease. The shorter the interval between injury and removal of the offending eye, the greater the prophylactic value of enucleation. Sympathetic involvement occurs most frequently between the 4th and 8th week after injury or operation. An attack is infrequent after 3 months and rare after 1 year. Once established the early administration of cortisone and ACTH is now considered the best available treatment. The use of antibiotics may be harmful as they kill the accessory flora and permit uninhibited multiplication of the virus of sympathetic ophthalmia.

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Biographical Note

Ernst Fuchs (1851–1930) was born in Kutzendorf, a village near Vienna where he received his medical education. After graduation he worked as Arlt's assistant for 6 years, and then assumed charge of the newly-formed department of ophthalmology at Liége. While there he submitted anonymously the prize-winning treatise on the prevention of blindness, surpassing Mules and Wilbrand, in a contest sponsored by the English Society for the Prevention of Blindness. In 1885 Fuchs succeeded Eduard Jaeger as director of the Second University Eye Clinic and became celebrated for his remarkable insight into the fundamental problems of ophthalmology. Salzmann, Meller, and Lindner were among his loyal assistants. The medical school, then at its zenith, included the Nobel Prize winners, Bárány, Landsteiner and Wagner-Jauregg. As pathologist Fuchs elucidated the processes of sympathetic ophthalmia, endophthalmitis septica, chalazion and pterygium; and as an astute clinician he isolated several new entities, such as epithelial dystrophy of the cornea, keratitis disciformis, superficial punctate keratitis, episcleritis periodica fugax and retinitis circinata. But his greatest gift to ophthalmology was his textbook. The admirable translations by Duane, begun with the second German edition of 1892, made the treatise a favorite among English-speaking nations. Fuchs was a masterful linguist and traveled extensively. In 1902 he delivered the Bowman Lecture at the Ophthalmological Society of the United Kingdom, and lectured in America in 1911, 1921 and 1929. Fuchs was the greatest ophthalmologist of his era, and his influence on ophthalmology is probably second only to Albrecht von Graefe.

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Book Reviews

Physiology of the Retina and the Visual Pathway, by G. S. Brindley, M.A., M.D. and edited by H. Barcroft, L. E. Bayliss, A. L. Hodgkin. $7.50. Edward Arnold, Ltd., London (exclusive United States agents: The Williams & Wilkins Co., Baltimore, Md.).

The primary interest of this book is the method by which the human visual pathway works. Discussion of the comparative physiology of the vertebrate eye is introduced only where it is needed to properly assess facts or inferences established for lower vertebrates in regard to validity for man.

There are 7 chapters in the 252 pages. The first 2 chapters deal with photochemistry and electrical activity of the retina; the 3rd with the central pathways of vision. The 4th and 5th chapters deal with sensory experiments, and the 6th with spacial, temporal and adaptational aspects of the visual threshold. The last chapter discusses the hypotheses and the testing of various physiologic aspects of color vision.

The table of contents is very descriptive so that one can refer to this table and easily determine the section which deals with a particular aspect of the subject.

Abundant internal cross references are in the text and there is a rather complete bibliography. No special section is devoted to anatomy but considerable anatomy is introduced in each section in an effort to allow better understanding of the varieties of functions.

The last 4 chapters consider the results of sensory experiments in which an essential part of the result is a report of the sensations of human subjects. There is a very interesting chapter which is devoted to a general discussion of the problem of drawing physiologic conclusion from sensory experiments.

This text can be recommended to the student who is anxious to obtain a good bit more than an introduction into the field of retinal physiology.

Irving H. Leopold

The Causes and Prevention of Acquired Myopia, by Tikasi Sato, M.D. 244 pp. Kanehara Shuppan Co., Ltd. Tokyo, 1957.

The author has been studying myopia since 1939. He favors the "refractive theory" over the "axial theory" of acquired myopia.

He says that the myopia of an eye can be ascribed to both congenital and acquired factors. "The congenital factors are found mainly in the ocular axis, while postnatal factors are found primarily in the crystalline lens." He presents massive amounts of evidence to support his thesis.

He says that the distribution of refractive errors does not follow a theoretical

curve. More people are emmetropic or close to emmetropic than one would expect. The adaptive action of the ciliary muscle on the lens is held responsible for concentrating the refractive error around emmetropia.

He believes that school myopia is caused by excessive near work. This causes the adaptive mechanism to push the eye toward the myopic side.

Tikasi Sato favors undercorrection of myopes to minimize accommodation for near work. He also favors the use of atropine drops. Paradoxically, he describes the use of pilocarpine drops in treating myopia, but he is uncertain as to its mode of action.

He seems a bit uncritical in his favorable mention of so many different therapies for myopia. For instance, he cites a report by Tokumitsu Tsutsui and Yukihiko Mitsui (1947). These men claimed an average improvement of 2.25 diopters in 34 cases of school myopia. The treatment was to have the patients focus alternately on a far point and a near point, thus making the "crystalline lens go through a kind of exercise."

The concepts of the author are not widely accepted by ophthalmologists in this country. The sheer volume of his work merits a respectful hearing and evaluation. He makes a forceful plea for his theory.

OWEN BELMONT

Antibiotics in Medicine, British Medical Bulletin, Vol. 16, No. 1. $3.25. The Medical Department, British Council, 65 Davies St., London W. 1, 1960.

The aim of this issue of the British Medical Bulletin is to provide the reader with established information on antibiotics. Much of the contained material cannot be found elsewhere except in the original papers. Dr. Garrod, the Chairman of the Planning Committee for the Symposium and also the Scientific Editor, states that no development in medicine has ever been at once so rapid and so complex. For this reason, it is extremely difficult to write in up-to-date fashion about this subject for anything which takes a long time both to write and to print is likely to be out of date even before publication. This symposium is up-to-date.

The Symposium consists of 15 chapters and an introduction by Dr. Garrod. The authors of these sections have a great familiarity with the material.

Abraham and Newton have discussed the chemical nature of antibiotics from the standpoint of those which are derived from amino acids or similar protein units; those which are derived mainly or partly from acetate and those which are derivable from sugars. There is another group of miscellaneous ones such as novobiocin, the structures of which have not been revealed in detail.

Biochemical investigations of antibiotics have been undertaken with the hope that an understanding of the mode of action might lead to a more rational development and design of chemotherapeutic agents. Up to the present, empirical screening procedures have been far more successful than any development resulting from this type of fundamental investigation. However, considerable information has been garnered by these studies dealing with the toxicity of anti-

biotics for cell wall synthesis, membrane permeability, protein synthesis and the like as discussed by E. F. Gale.

Organisms may resist antibiotics by virtue of not possessing a system which responds to the antibiotic or by having a surface which does not allow the antibiotic to penetrate or the cell may possess some means of destroying the drug before it produces its toxic effect. M. R. Pollock has suggested, in his section on the mechanism of drug resistance, that a rational and practical basis in dealing with the problem of drug resistance might include attempts to prevent the appearance of mutation and genetic combinations, reduce the selection pressures allowing mutants to multiply at the expense of the original sensitive cells and inhibit specifically the formation of enzymes responsible for destroying the drug or providing alternative drug-resistant metabolic pathways.

L. P. Garrod and Scowen consider the principles of therapeutic use of antibiotics. Included in their section is the necessity of bacteriologic diagnosis, the indications for sensitivity testing, the importance of proper choice of preparation and route and the duration of therapy, and also the accessory factors. Antibiotic treatment sometimes fails because it cannot succeed alone and other measures necessary for its success have been neglected. In this chapter, as in others, there is very little specific mention of the ophthalmologic indications. Here one cannot always be guided by bacteriologic analysis.

Considerable space in all sections is devoted to the penetration into the central nervous system which provides a barrier very comparable to that of the blood aqueous barrier.

There is a very thorough discussion on the laboratory control of antibiotic therapy by J. C. Gould devoted essentially to the value and the proper means of doing and selecting sensitivity studies.

Robson and Buttle consider the pharmacology of the various forms of pencillin such as benzyl penicillin, procaine penicillin, phenoxymethyl penicillin, streptomycin, neomycin, viomycin, cycloserine, kanamycin, chloramphenicol, the various tetracyclines, erythromycin, novobiocin, vancomycin, antifungal antibiotics such as nystatin, amphotericin B and griseofulvin; polypeptide antibiotics such as bacitracin, polymixin, tyrothricin and a number of antibiotics which have influence on malignant disease. The penetration of each of these compounds and their distribution to body tissues and fluids is carefully considered. However, there is no specific mention of these pharmacologic aspects in ocular tissues and fluids.

The general principles of the rationale and management of combined therapy is thoroughly discussed by B. W. Lacey. The preventive use of antibiotics in medicine and in surgery is considered by Bywaters and Taylor. There are many hazards and drawbacks of prophylactic antibiotics but there are definite places where their use is indicated on the basis of our present knowledge. In general, antibiotics should not be used prophylactically in clean surgical cases. It is not proper to use these agents in order to protect one's self because of fear of litigation or as a substitute for good surgical technique. Most of the evidence which is available on the use of antibiotics prophylactically in surgery has not substantiated its value. There is no data in these articles on the value of test trials with

prophylactic antibiotics in ophthalmic surgery. Taylor has concluded that, in clean surgical procedures, the administration of antibiotics not only fails to reduce the incidence of infection but may cause serious iatrogenic complications and may, in the long run, facilitate the breeding of resistant bacteria.

There is no doubt that the introduction of antibiotics and awareness of their complications have awakened a renewed interest in the basic principles of the surgical craft.

There are chapters on the specific management of infections due to tubercle bacilli; on the dangers of antibiotic treatment; on the present search for new antibiotics and on the laboratory uses of antibiotics as well as a specific one dealing with the clinical problems of drug-resistant pathogen.

Although there is very little attempt to correlate the available data to ophthalmology in this excellent symposium, each section contains information which would be of considerable value to every ophthalmologist. Most of the sections represent the latest accumulation of data and contain much which would refresh the clinical ophthalmologist's knowledge of antibiotics as well as fortify him for selection and management of his patients with ocular infections.

IRVING H. LEOPOLD

Glaucoma, edited by FRANK W. NEWELL, M.D. Transactions of the Fourth Conference, sponsored by Josiah Macy Jr., Foundation, Princeton, N. J., March 8, 9, and 10, 1959. $8.00. Madison Printing Company, Inc., Madison, N. J.

The fourth session of the Josiah Macy, Jr., Foundation conference program on glaucoma was devoted essentially to the structure of the trabecular apparatus, ciliary epithelium, and to pathologic findings in eyes with primary glaucoma. The ultrastructure of the trabeculum was studied by means of the electron microscope. In addition, the trabecular structure was considered by various histochemical stains and the relationship of the ciliary epithelium to aqueous humor secretion as it appeared in the electron microscope was also presented.

Those leading the discussions were Drs. Garron, Holmberg, Ashton, Pappas, and Kornzweig.

A good bit of this information has been published elsewhere, *e.g.*, in Volume 62 of the A.M.A. Archives of Ophthalmology, December, 1959. However, the great appeal of these presentations of the Macy Foundation are the frequent questions and discussion presented by the many participants. The leader of the discussion is constantly interrupted by cogent questions. One cannot help noting how many provocative questions were placed before the group by Dr. Fremont Smith. It is surprising how many items are clarified by the questions. In other areas the questions simply point up the real lack of information.

The illustrations are superb.

Dr. Ashton has reviewed the many variables which can be responsible for potential errors in an attempt to identify mucopolysaccharides by histochemical stains. Ashton's work did not support the claim that hyaluronidase sensitive mucopolysaccharide exists between openings in the meshwork. Ashton was also unable to confirm Zimmerman's finding of mucopolysaccharide in the corneal scleral meshwork of human eyes. This is an excellent example of an area where

considerably more work is necessary and where the electron microscope may prove to be of great help.

Dr. Pappas' work demonstrating vacuoles either in the cytoplasm or in the cells of the ciliary epithelium suggests that something is actually taken back from the posterior chamber into the cells as one possible explanation of the findings. Dr. von Sallman recalled that years ago, Meller, Ma and Pillat demonstrated the absorption by the ciliary epithelium of substances introduced into the vitreous such as India ink, soluble ion salts, cod liver oil and blood.

Smelser has suggested the concept that secretion of the ciliary body may be a process of putting in some substance and taking others back selectively as the kidney does.

There is no doubt that one has to relearn anatomy and histology in view of the advent of the electron microscope, and these discussions which tie in ultrastructure with attempts at physiologic explanations of function make the learning of the latest presentations of anatomy rather a provocative task.

This Fourth Symposium, as the previous ones, is a well edited text which allows the general ophthalmologic public to share the intimacy of the small group as they work over the fine aspects of the glaucoma problem. As one reads, he frequently has the feeling that he is actually present at the symposium. This is no doubt due to the recorded conversations. In our rush for short-cuts to the acquisition of information, this reviewer sincerely hopes that we find time to appreciate and demand this type of communication.

IRVING H. LEOPOLD

An Investigation of Optical Corrections for Enabling Patients With Low Visual Acuity to Read, by JAN KAREL PAMEIJER. 121 pp. N.V. Uitgevers-Maatschappij, Æ. E. Kluwer, Deventer-Antwerpen.

This is a well thought out approach to the problem of prescribing visual aids for the partially sighted.

The author believes that the simplest way to express visual acuity is in percentage. He also emphasizes that it is important to make an advance assessment of the magnification necessary before having the patient try a visual aid. This prevents the prescribing of a device which has a magnification greater than necessary. He discusses four ways to do this.

He then describes the visual aids available under four headings: (1) telescopic spectacles, (2) strong positive glasses, (3) stand magnifiers and hand magnifiers, and (4) Keeler's telescopic glasses, for reading only. He presents the practical application of these devices, along with detailed case histories of patients.

Finally, he summarizes the equipment necessary for a low vision clinic and his procedure in examining a patient. He emphasizes that an hour and a half should be allowed for the first examination.

The translation is good and makes for pleasant reading. Anyone who is thinking of working with partially sighted patients will benefit from a reading of this book.

OWEN BELMONT

Current Review

CURRENT STATUS OF CLINICAL ELECTRORETINOGRAPHY

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In 1865 Holmgren[1] first noted that the electrical status of the eyeball changed when light fell upon it. As long ago as 1877 Dewar[2] recorded the same type of potential from the human eye.

This phenomenon has been intensively studied since then, and has come to be known as the electroretinogram or ERG. Early studies were hampered by technical difficulties, and it was not until the 1940's, primarily as a result of the introduction, by Lorrin Riggs,[3] of the use of a contact lens to support the recording electrode in proximity to the eye, that reproducible ERG's were attainable.

Application of the phenomenon to clinical problems, first systematically attempted by Gosta Karpe,[4] has occupied a number of laboratories for the past 15 years.

Despite this effort, and in the face of an avalanche of papers in the literature dealing with the subject, the technique has not come into wide general use in clinical ophthalmology. The chief reason for this is that the ophthalmologist has, in the ophthalmoscope, an instrument far less esoteric than the ERG which will usually give adequate information about the retina. If the internist were able to visualize the coronary circulation with as much facility as we can observe the retinal vessels, the electrocardiogram would not be as dominant a feature of cardiologic practice as it is at present.

The possible applications fall into four classes:

1. Those instances—as cataract, where ophthalmoscopic observations is precluded.

2. Those instances where the retinal pathology is not grossly apparent, consisting of subtle chemical or physical changes which do not cause ophthalmoscopically visible lesions. Total color blindness is a good example.

3. Those instances where the fundus may present an ambiguous appearance—for example in retinal pigmentary degenerations, where the ERG will aid in the differential diagnosis between primary and secondary retinitis pigmentosa and between retinitis punctata albescens and fundus albipunctata.

4. Those instances where cooperation in performance of subjective tests is unobtainable, such as in children or where malingering may be a factor.

The importance of clinical electroretinography, therefore, must rest upon the technique's ability to provide information not available by routine methods of

examination. This paper will discuss those clinical problems in which this is true at present, as well as future possibilities.

The electrical response to a light stimulus of the eye is a polyphasic potential. Einthoven and Jolly, in 1908,[5] first designated them by letter, and the nomenclature has remained the same since then. The first observable response of a normal eye is a negative wave, the a-wave, which is followed by a positive deflection of greater magnitude, the b-wave. If the light is continued at a sufficiently bright level, for the correct period of time, a c-wave, of positive sign develops. The cessation of light stimulation evokes a d-wave, or off effect.

It has been shown that the conformation of the response can be modified by changes in the character of the stimulating light, the functional status of the retina, including the state of dark adaptation, and by variation in systemic blood pressure, application of drugs, temperature changes and other factors.

The complexity of the wave form and the fact that each of the component parts of the wave may be selectively altered by different conditions have been interpreted to mean that the potential as recorded from the surface of the eyeball is actually a summated mass response, made up of a number of independently fluctuating variables.

The presence in the retina of a variety of structural and functional cell types, when viewed in conjunction with the complex wave form, has caused speculation and investigation of the part played by each of the several cell types in the production of the ERG.

The work of Ragnar Granit, which is well reviewed in his monographs of 1947[6] and 1955,[7] and that of Werner Noell,[8] have consisted in large part of studies of the effects of drugs and physical agents upon the ERG. By correlation of histologic changes to alterations in the retinal potential, and by study of the relationships of the several components of the ERG to optic nerve function, as influenced by chemical agents, and of the temporal relationships between the several components, these investigators have attempted to localize the site of origin of the ERG.

Another approach to the problem of which elements of the retina are responsible for the ERG has been the study, with micro-electrodes, of the characteristics of the responses at various levels of depth within the retina. The reports of Tomita, Ottoson and Svaetichin, Brown and Wiesel, and Brindley, which are well reviewed by Brindley in his recent book,[9] have been outstanding in this area.

From all the evidence collected to date it seems fairly certain that the c-wave arises in the pigment epithelium and that the a-wave and b-waves, which are the components usually recorded in humans, arise in the region of the bipolar cells and the rods and cones. Certainly, the ganglion cells do not seem to be directly involved in the production of the ERG.

The importance of this aspect of the problem to clinical ophthalmologic problems is apparent. If we know which cells are responsible for the ERG, we will know that in those diseases where these cells are affected we may expect help from the ERG in diagnosis and prognosis. Similarly, we may infer from an abnormal ERG that the disease process in a given individual lies within these cells.

The recent findings of Lindsley[10] and Potts[11] relative to the time relationships between ERG and optic nerve and lateral geniculate body responses indicate the responses in the higher visual centers *precede* the development of the b-wave. This would certainly indicate that the ERG, or at least the b-wave, is a result of retinal activity, but not necessarily the actual phenomenon responsible for higher perception of vision.

The ERG is an evoked response—that is, it must be produced by a light source falling upon the retina. The response characteristics is dependent, therefore, upon two general factors; the stimulus and the retina, including its functional milieu. Each of these two factors, in addition, is variable in terms of each of its several parameters.

Changes, therefore, in the intensity, duration, spectral composition, size of field, focus of field, rate of repetition or rise time of the stimulus will alter the response. Similarly, physiologic variation in ocular status, such as the level of dark or light adaptation, pupil size, level of activity of higher nervous centers and general physiologic factors such as blood pressure, will also vary the response. It has even been reported recently by Allachverdjan[12] that it is possible to affect the ERG by a conditioned reflex.

All of these factors, must, therefore, be considered and controlled, in such a manner as to keep them as constant as possible, before any change in the ERG may be considered due to a particular retinal disease.

In addition, it must be kept in mind that the record obtained is also a function of the characteristics of the recording system. The amplifier and writing device used, if not of a type suitable for utmost fidelity, will lose certain components of the response while artificially exaggerating others. This is not of overweening significance in the gross scotopic ERG, but will assure greater importance with greater need for observation of fine detail.

In the course of study of the influence of variation in adaptation status and spectral composition of the stimulus, it was first shown by Motokawa and Mita,[13] in the case of the b-wave, and by Armington, Johnson and Riggs,[14] in the case of the a-wave, that each of these portions of the response is actually a double response, and it is quite likely, as has been shown by Auerbach and Burian,[15] that each consists of an early portion due to photopic function and a later one due to scotopic activity. This means that in keeping with the duality of the retina known to exist from other physiologic studies as well as the anatomical evidence, there are two ERG's, a photopic and a scotopic.

To return to the clinical applications of the ERG, therefore, we have to face the problem of standardization. Since the ERG, as discussed above, will change with any alteration in the character of the stimulus, we must first of all decide upon a single, or perhaps, in view of the duality of the response, a double set of standard conditions, each of which will serve best to produce the type of response with which we are most concerned.

This is exactly what Gosta Karpe did, in 1954.[4] His monograph, dealing with the findings in a group of normal cases and a variety of clinical diseases, was the first such systematic study and is the basis for all clinical electroretinography.

His technique consisted of recording by means of an electrode inserted in a

contact lens, the responses induced by flashes of $\frac{1}{25}$ second of an incandescent light source. The patient, who had generally been indoors for a period of time, was dark adapted for 5 minutes. A dull red glowing fixation light was usually on between stimuli. The stimuli were presented by manually pressing a button. This was, in essence, a partially dark adapted, scotopic record.

More recent studies in several laboratories have generally used more intense light sources, frequently of an electronic flash type (stroboscope), which produces extremely short and intense bursts of light.

The influence of the duration of dark adaptation has also been considered, and longer periods of adaptation are now generally used, with a standard duration of pre-adaptation to a light adapting area. Filters are used to produce monochromatic stimuli.

The influence of the shape of the contact lens has recently been studied by Sundmark,[16] and is another factor to be considered.

Having decided upon a standard set of conditions, of stimulus and patient and retinal *gestalt*, and ignoring for the present any consideration of the physiologic implications of the responses produced by this or any other set of conditions, we may record ERG's from a patient. Now, just what does this method have to offer the clinician at present?

It has something to offer in those patients in whom ophthalmoscopic examination is unsatisfactory, or impossible. The most frequent instance of this situation is in cataract. The same situation may arise in patients with corneal or vitreous opacity.

In clinical practice, when the cataract patient's fundus cannot be observed because of the density of the lens, an estimate of the retinal functional ability is usually made by the patient's ability to project accurately the location of a light to differentiate between two points of light, or, frequently, to appreciate color differences.

In a series of patients with cataracts, our laboratory has found that the ERG is more sensitive than these subjective tests in detecting retinal pathology. In those instances where the subjective tests and the ERG were at variance, the ERG was usually more accurate. Karpe and Vainio-Mattila[17] had reported similar results earlier.

The method of recording the ERG in a dark adapted state results in a record which is an indication of the functional integrity of the entire retina. In clinical practice, however, the visual result following cataract extraction depends not only upon the state of the entire retina, but more specifically upon the condition of the macular area. It is of importance, therefore, to try to evolve a test of macular function.

Anatomically, the rods outnumber the cones in the human retina, 125 million to 7 million. The total number of cones in the fovea, including about 1.5 mm. is only 115,000. Thus, the numerical superiority of the rods alone, indicates that the "uncovering"—in the word of Granit, of the cones' system response from the overwhelming magnitude of the rod response will be difficult. It has been assumed in the literature of the retina for many years that the cones were the photopic elements and the rods the scotopic. This is probably true. It must

be stated, however, that as the result of recent work by Tansley[18] and also by Davis and Arnott,[19] it has been shown that animals with purely rod retinae may develop, under certain conditions, electroretinographic responses typical of photopic systems, and conversely, that animals with pure cone retinae may develop responses typical of scotopic states. Thus, it is probable that the anatomy of a visual cell is probably not an absolute guide to its function; under proper conditions rods may act like cones and *vice versa*.

Recognizing, therefore, that the terms rod and cone do not necessarily indicate scotopic and photopic respectively, but that in all likelihood the photopic response is more likely to be a key to macular function than that of the total retina with its preponderance of rod function, several attempts have been made to emphasize the photopic or macular response to provide more accurate information about the macular function. These have been:

1. Limitation of the field of stimulation to the macular area. This has not been successful, since there is spread of the stimulus, either through scatter of the light or neuronal spread, or both, so that effectively there is no limitation. This has been shown by Asher,[20] who limited the stimulus in such a manner as to stimulate only the optic disk. Despite the fact that the light was falling upon physiologically inactive tissue primarily, secondary spread of the stimulus evoked a quite normal ERG.

2. Selection of stimulus and adaptation parameters conducive to relative suppression of the scotopic function as compared to the photopic.

The photopic system is relatively more sensitive to the long wave length end of the spectrum than the scotopic, and is capable of responding to repetitive stimulation at a higher rate. The photopic ERG is also relatively more pronounced than the scotopic response in light adapted state, whereas the scotopic elements become more evident in the course of dark adaptation. These facts have been the basis for a number of clinical studies in which the ERG under conditions which should provide the maximum degree of information concerning central retinal functional integrity have been tested in normal eyes and eyes with macular disease.

The results, as recently summarized by Jayle,[21] have been confusing and often contradictory.

Using a deep red filter, the author, with Basar and Kornzweig,[18] studied the responses of a group of patients with marked senile macular degeneration and found a marked diminution in response. This finding has been confirmed by Bessiere and Chabot,[22] Ruedemann and Noell,[23] and by Jayle,[21] but Francois *et al.*[24] and Rendahl[25] were unable to find the same results.

This disparity may be due to differences in technique, or perhaps to variation in type of case. Certainly, in our series, when there is severe macular disease, of the senile degenerative type, there is a marked reduction in the response to long wave length stimuli.

In an attempt to elucidate this subject, we have recently destroyed, with the use of the Meyer-Schwickerath photocoagulator, the maculae of a number of monkeys. The ERG was not affected. This, when coupled with our clinical findings, leads us to believe that in the advanced senile macular degenerations

where the ERG response of the photopic system is reduced, there is widespread disease of the retina, involving a large proportion of the photopic elements, macular and extramacular, and that this is the explanation for the changes in the ERG.

As found also by Jayle,[21] the scotopic response in these patients seems intact.

Acute lesions, such as chorioretinitis do not seem to affect the photopic system deeply or widely enough to produce noticeable effects in the ERG.

The adaptometric curve of patients whose red response is diminished shows a quantitative loss of the cone fraction of dark adaptation, adding to the evidence of a widespread loss of photopic function.

A second approach to investigation of the photopic response has been made through the use of repetitive, or flickering stimuli. The photopic system is capable of producing individual responses to stimuli presented to it at a rate faster han that which the scotopic system can follow. Subjectively this is evidenced by a higher critical fusion frequency (the frequency at which the flashes can no longer be discerned and the light appears to be constant) in the fovea area than elsewhere in the retina.

By using stimuli of a flickering nature, therefore, it is possible to delineate the scotopic from the photopic elements of the response. The photopic elements respond to a more intense stimulus repeated at a faster rate while the scotopic elements are inhibited by the light adaptation due to the intense repeated stimuli and are unable to follow the fast rate of presentation.

This work, first undertaken by Dodt and Wadensten[26] in 1954, and amplified more recently by Wadensten[27] has shown that in total color blindness, where the photopic system is poorly developed, that the ERG photopic elements are absent.

Henkes,[28] with a system of selective amplification he devised, in conjunction with van der Tweel and van der Gon[29] has also studied photopic flicker responses and has found that it is possible to judge the cone system functional ability by this technique, which is not recordable by ordinary means.

Jayle[21] reports that in patients with severe senile macular degeneration the flicker fusion frequency is diminished.

The net result of this to the clinician, therefore, is that the ERG will certainly provide information relative to the general functional integrity of the retina when ophthalmoscopy is impossible due to opacity of the media. The ERG is more reliable than the subjective tests usually used, and in all likelihood the ERG may be depended upon to detect not only such gross lesions as retinal detachment or circulatory disturbances of great magnitude, but will indicate far advanced macular degenerations, if testing circumstances suitable for emphasizing photopic elements are used. It is, therefore, very useful in preoperative analysis of patients with cataract, especially unilateral, and of corneal and vitreous opacities.

The second type of case in which the ERG is of use to the clinician is in retinal detachment.

Rendahl,[30] in 1957 reviewed 277 retinal detachments studied by Karpe and

himself, and the author, studied a series of 50 cases.[31] Both have found that the ERG is useful in prognosis of the disease.

Other authors, reporting on smaller series, have reported with less enthusiasm on the prognostic value. Perhaps some of the lack of agreement is caused by disagreement on what constitutes a successful therapy of a case. It is my opinion that the essential criterion for success in therapy of retinal disease is recovery of function. Mere reattachment of the retina, while difficult in itself is of no value to the patient if the retina is nonfunctioning. Since the ERG is a measure of retinal functional ability, it does provide a measure of prognosis for recovery of function, in such a disease, however, where the restoration of vision is dependent not only upon the retinal vitality by the area of the pathology and the ability of the surgery to re-establish anatomical integrity, retinal vitality cannot be expected to be the sole criterion for success, in terms of vision.

The large number of variables inherent in this disease make it imperative that a statistical correlation of a very large series of cases must be made before any conclusions may be drawn.

In siderosis of the retina Karpe[32] first reported that early in the course of the disease there occurred an initial increase, followed by a diminution in the b-wave amplitude. This decrease has been found in several cases in our laboratory's experience, and has been of significance in determining the necessity for removal of a metallic foreign body, by indicating the presence of toxic effects upon the retina. In one of our recent cases, where a minute steel foreign body has resisted two attempts to remove it, the diminution in ERG has been accompanied by a reduction in dark adaptation ability, also significant of widespread retinal functional loss. These indications of retinal pathology have indicated the necessity for another attempt of removal of the fragment.

In cases where the foreign body is easily removable, the ERG will not be a factor in the clinical management of the case, since the object will be removed. In those instances, however, where removal is difficult or the foreign body has been present for a protracted period of time, the decision concerning the necessity for removal must depend in part upon the estimate of the influence of the foreign body upon the retinal status and the ERG will be of assistance in making this decision.

In hereditary retinal degenerations, or "tapeto-retinal degenerations," the status of the ERG as a clinical aid to diagnosis is presently somewhat confused.

It was first reported, by Karpe[4] and a number of others, that in all cases of primary retinitis pigmentosa, regardless of the severity or duration of the disease, no electrical response could be recorded. This was even true in a 9-month-old infant in a suspect family. In contradistinction to this, in "secondary" retinitis pigmentosa, including luetic choroiditis which resembles the primary disease in ophthalmoscopic appearance, normal or moderately reduced ERG's were found. This remarkably simple finding seemed to provide a wonderful means of telling the two types of retinal degenerations apart. Unfortunately, it was too simple. Reports have been published in the past several years, primarily as a result of the utilization of more powerful light sources as stimuli, of patients with retinitis pigmentosa with subnormal and, even totally normal ERG's.

There have been publications which indicate that the ERG in certain family groups with retinitis pigmentosa varies among individuals according to the severity of the visual field loss.[23]

Henkes[28] has reported being able to record, with selective amplification, a degree of photopic response in a case of primary retinal degeneration in which no response could be obtained by usual means.

This is not true, however, in all cases, including a number in our laboratory, where in response to a test stimulus of 3.2×10^6 foot candles, early cases produced no response. This intensity is greater than that used in most of the other reports.

A definitive statement cannot be made at this time, and will not, probably, be able to be made until such time as a number of cases have been followed with serial ERG's throughout the life history of the disease. At this point, I believe, it is best to say that the ERG is greatly reduced or absent in the vast majority of cases of primary retinitis pigmentosa even before clinical or ophthalmoscopic evidence of disease and only moderately diminished or normal in those infectious and toxic diseases which cause ophthalmoscopic pictures similar to retinitis pigmentosa. It is my personal opinion that a further classification and subdivision of the large group of disease entities now called retinitis pigmentosa will be necessary, based upon consideration of all the factors relevant to the disease, including family history, adaptometry, ERG and visual field changes. We have observed that each of these features varies individually and apparently independently of the others in each individual case, although the classical absence of ERG is most often recorded in the patient with tubular fields, loss of adaptation ability and characteristic fundus picture.

In a family currently under investigation we have found that a female carrier of a sex-linked type of retinitis pigmentosa with perfectly normal vision and adaptometry had an ERG response characterized by a lack of increase in the scotopic portion upon dark adaptation.

Modification of the testing conditions to include those which favor the photopic elements, as well as improved techniques for registration of minimal responses will result in reduction of the number of "extinguished" ERG records. I believe that when no response can be detected it would be better to use the term "non-recordable."

Among related disease states, Franceschetti and Dieterle[33] have reported the differentiation between retinitis punctata albescens and the relatively innocuous fundus albipuntatus with hemeralopia on the basis of the ERG. The ERG was absent in the former and normal in the latter.

A differentiation between the infantile and later types of amaurotic family idiocy has been reported, indicating that the infantile types, where the pathology is primarily in the ganglion cell layer is characterized by less severe impairment of the ERG than in the later types, wherein the histopathologic damage involves also the outer cell layers.

Choroideremia has been reported[34] to produce an absence of response. In a family observed in our laboratory one member with only minimal fundus changes

showed a subnormal response while more severely affected individuals had no measurable response.

For the clinician, the significance of these findings lies primarily in the ability of the ERG to aid in the differential diagnosis of primary from secondary retinitis pigmentosa.

Another clinical entity in which the ERG is of interest is color blindness. Characteristic variations in protanopia have been reported by Armington[35] and by Francois, de Rouck, and Verriest[24] as well as by Rendahl.[36] Heck and Rendahl[37] have recently noted a lack of a separate subcomponent of the b-wave in protanopes, and in deuteronopes. In total color blindness Goodman and Bornschein[38] have reported absence of all photopic response.

In night blindness, both congenital and that due to vitamin A deficiency,[39] there is a loss of the scotopic component primarily, although the responses of the avitaminotic retina are totally abolished while in congenital night blindness the photopic component may be demonstrated.

In vascular lesions of the retina itself, either arterial or venous, reduction in the b-wave is the most prominent feature. Henkes[40] has studied a number of cases of this type of disease, and has found it possible to judge the prognosis of a given case by the ERG character.

Henkes[41] has also reported responses of amplitudes greater than normal in patients with systemic hypertension whose fundi were normal. He and his coworkers[41] have also investigated the effects of drugs which lower the blood pressure in hypertension upon the ERG. They conclude that the retinal blood supply can be compromised by reduction in blood pressure.

Diabetic retinopathy usually does not compromise the ERG amplitude until the disease has reached far advanced stages, such as retinitis proliferans and detachment.

In glaucoma most authors report a relatively normal ERG except in far advanced degenerating eyes. This is in keeping with the histopathologic findings indicating that the disease attacks the ganglion cells and the optic nerve fibers before the visual cells. Since the ganglion cells probably do not participate in the production of the ERG, it is not to be expected that their disease would affect the response.

Melik-Musjan,[42] however, has recently found a diminution in a response to a red stimulus in early glaucoma, while Henkes[43] has reported an alteration in the response to blue stimuli.

Severe retinal damage due to quinine or methyl alcohol intoxication will produce alterations in the ERG.

As discussed by Karpe and Zetterstrom[44] and, later, by Schappert-Kimmijser, Henkes and van den Bosch,[45] use of the ERG in children with poor vision whose fundus may not be markedly abnormal will give evidence of markedly abnormal retinal function. Karpe and Zetterstrom[44] on this basis have described a new entity, congenital retinal dysfunction.

In sum, therefore, there are a number of areas in which the electroretinogram can be of assistance to the ophthalmologist.

It has been my purpose to describe those applications which seem to me to be of most current interest for the clinician. The great mass of fascinating studies of ocular electrophysiology are ignored, since their clinical significance is as yet undetermined.

The ERG, today, will allow for estimation of retinal and, to some degree, macular function when the opthalmoscope is rendered useless by medial opacities, and will determine retinal functional status in situations where the ophthalmoscope gives little or no information.

The technique of testing, although hardly standardized, is in any case not terribly complex; with a minimum of modification the average electroencephalographic unit of a hospital can be utilized for a gross scotopic recording. Finer detailed work, including a search for minimal responses and estimation of flicker fusion frequencies and photopic elements will require more elaborate installations. Wider application of the test will certainly improve our diagnostic and prognostic capabilities.

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Special Article

COMPLICATIONS OF PHENOTHIAZINE TRANQUILIZERS: OCULAR SIDE EFFECTS

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The increased number of phenothiazine derivatives which have been popularly used, and the concomitant increase in the side effects, both systemic and ocular, found to accompany their use demand a conscientious appraisal of this subject. Ophthalmologists share in this extensive utilization of the phenothiazine agents, prescribing them for relief of emotional stress, the prevention or control of nausea and vomiting, and for their potentiating effect on barbiturates, opiates, and anesthetics. They should, therefore, be familiar with the potential side effects of the various drugs.

References to the ocular consequences of this therapy, however, have been generally limited to journals unrelated to the field of ophthalmology, and consequently, the practitioner has not been able to place this problem in a context which could most satisfactorily serve in the establishment of effective diagnoses and treatment. The author, however, has witnessed several instances in which this problem has been manifest and, accordingly realized that a contribution to the understanding of this subject could be provided by a review of the literature with regard to ocular side-effects which have been experienced in the course of treatment with this family of drugs and, in addition, the citation of an illustrative case in which a patient elicited an initially unrecognized response to one of the phenothiazines which had been used as an adjunct to the prescribed medication. It was deemed most practicable to collectively evaluate the information related to the period during which these drugs were initially developed and popularized and supplement this by specific references to current sources.

The list of available phenothiazine drugs includes:

Generic Name	*Trade Name*	*Generic Name*	*Trade Name*
Chlorpromazine	Thorazine	Promethazine	Phenergan
Fluphenazine	Prolixin, Permitil	Thioperazine	Vontil
Mepazine	Pacatal	Thiopropazate	Dartal
Methoxypromazine	Tentone	Thioridazine	Mellaril
Perphenazine	Trilafon	Trifluoperazine	Stelazine
Pipamazine	Mornidine	Trifupromazine	Vesprin
Prochlorperazine	Compazine	Trimeprazine	Temaril
Promazine	Sparine		

Evidence of the frequency with which these tranquilizers are presently used is reflected in the analysis of prescription trends in recent years. In 1959, tran-

quilizers were the third major ingredient employed in prescriptions, not far behind antibiotics and barbiturates. Soon after the popular adoption of the first phenothiazine tranquilizer, chlorpromazine (Thorazine), it became apparent that adverse effects developed in a small percentage of patients, examples of which were found to be jaundice, agranulocytosis, skin rashes, photosensitivity, pruritis, and neurologic symptoms. Although all of these responses have not been reported with each of the 15 phenothiazine agents listed, we may assume that they may be induced by any one of the drugs because of their similar chemical structure. Jaundice and agranulocytosis have been observed with the use of chlorpromazine, mepazine, perphenazine, prochlorperazine, promazine, and trimeprazine; promethazine has also been associated with agranulocytosis. Allergic dermatitis has appeared after the administration of chlorpromazine, mepazine, perphenazine, prochlorperazine, thiopropazate and trifluprom azine.[1-5]

CASE REPORT

A specific illustration of this problem is that of a 9-year-old boy with toxoplasmic uveitis who had experienced nausea following spiramycin, an adverse emotional reaction to his hospitalization, and decreasing vision; his behavior was noted to be depressed, nervous, and uncooperative. Prochlorperazine (Compazine) had previously been prescribed for this child during a period encompassing 5 months at home and three hospitalizations, in doses ranging from 10 to 20 mg. per day orally, as a consequence of which the behavior disorder was improved. This regimen was established within the limits generally recommended for emotional problems in children of this age, the dosage for which has ranged up to 25 mg. per day, orally.

During this most recent admission, the child developed more acute emotional disturbances, characterized by refusal to take any medication and general inaccessibility. The resident physician ordered the administration of Compazine intramuscularly, 10 mg. to be given twice daily. The medication was continued for 2 days. Within 12 hours after the last dose, the patient experienced various periods of drowsiness and restlessness followed by intermittent attacks of opisthotonus, torticollis with the head turned to the left, spasm of the muscles about the mouth with the mouth drawn to the right, trismus, dysphagia, excessive body movements, carpopedal spasm, dystonic movements of the upper extremities, oculogyric crisis and cyanosis, but no loss of consciousness.

Initially regarded by the resident and attending staff physicians as an atypical convulsive episode requiring neurologic consultation, no definitive diagnosis was established. Following the examination of the patient by the author, the case was recognized as a neuromuscular reaction to Compazine. A hypnotic dose of paraldehyde was prescribed for rectal administration, 12 hours after which no abnormal neurologic signs remained.

THE EXTRAPYRAMIDAL MOTOR SYNDROME; OCULOGYRIC CRISIS

The neurologic side effects of phenothiazine therapy may vary from mild loss of skilled muscle movements to actual parkinsonism-like activity. In this category

is a severe extrapyramidal convulsive syndrome which should be familiar to the ophthalmologist, one ocular complication of which is oculogyric crisis.[5-12]

To date, neuromuscular reactions have been known to occur with 10 of the 15 phenothiazine tranquilizers on the market: chlorpromazine (Thorazine), fluphenazine (Prolixin, Permitil), mepazine (Pacatal), perphenazine (Trilafon), prochlorperazine (Compazine), promazine (Sparine), promethazine (Phenergan), thioperazine (Vontil), thiopropazate (Dartal), and trifluprom azine (Vesprin).

The syndrome is characterized by sudden and recurrent attacks of muscular spasm which may involve any of the skeletal muscle groups and last a few seconds or several hours. The patient remains conscious during and between attacks, is apprehensive and disturbed, and may display marked motor restlessness and inability to sit still (acathisia). Oculogyric crisis is seen with spasm of the ocular muscles, either as an isolated manifestation of phenothiazine toxicity or associated with spasms of other muscle groups. Tonic contractions of the back, shoulder, and neck muscles cause opisthotonus and torticollis; the head may be turned to one side. Facial and jaw muscle spasms produce risus sardonicus and trismus; a mask-like facies has been described in other patients. There may be loss of control, severe protrusion, or athetoid movements of the tongue. Acute laryngospasm with respiratory distress has occurred, during which, on occasion, tracheotomy has been contemplated or actually performed before the reaction was recognized. Involvement of the limb muscles causes a loss of associated movements in walking, flexor and extensor spasms of the extremities, hyperreflexia, and dystonic or cog-wheel movements of the upper extremities.

This bizarre neurologic syndrome has been the cause of alarm and confusion to the uninformed observer, by whom erroneous diagnoses such as hysteria, tic, epilepsy, bulbar poliomyelitis, encephalitis and tetanus have been made. Failure to recognize these complications by the physician has led not only to incorrect diagnoses but to undue concern and unnecessary diagnostic and therapeutic measures.

It is important to note that the extrapyramidal motor symptoms are not necessarily a consequence of excessive dosage of the phenothiazine drug, but may appear after one or several days of normal dosage. In addition, signs of extrapyramidal hyperactivity may occur in a patient who has been receiving the phenothiazine drug without adverse effects, following the sudden increase of the dosage over the previously prescribed amount. This type of response was described in the preceding case report. The initial symptoms may be manifest either immediately or within 16 hours after the last dose of the drug.

This extrapyramidal reaction occurs more frequently and more acutely in children than in adults. Furthermore, complications such as infections or dehydration make the child even more susceptible to the toxicity of the phenothiazine. Typical cases of parkinsonism resulting from phenothiazine therapy, on the other hand, have been observed in adults, but are rare in children. Emphasis should be placed on considerations such as this which serve to facilitate the recognition of these symptoms.

Proper treatment of the phenothiazine-induced extrapyramidal syndrome is

dependent on recognition of the etiology, for cessation of the therapy affords complete recovery, usually within 12 to 24 hours. Authors have reported effective control of these seizures with barbiturates, chloral hydrate, intravenous caffeine and sodium benzoate, and anti-Parkinson drugs[13] including Cogentin (bentropine methanesulfonate), Kemadrin (procyclidine), Parsidol (ethopropazine), and Artane (trihexyphenidyl hydrochloride). A central ganglioplegic agent in the form of an antihistamine which can be given parenterally, diphenyhydramine (Benadryl) was reported recently as exercising both a highly effective and prompt control.[14] Chlorphenamine is a similar agent which also can be given by injection.

The first phenothiazine preparation which was found not to induce extrapyramidal overactivity was thioridazine (Mellaril). This derivative is a relatively weak phenothiazine and has a limited antiemetic action. One anomalous characteristic of thioridazine is that while extrapyramidal signs are not induced, certain serious eye complications may be caused which are described in the succeeding section.

To my knowledge there have been no deaths reported in patients with the extrapyramidal syndrome. There is a report,[15] however, of a fatal convulsion in a young adult who was given one dose of perphenazine (Trilafon) after an elective operation.

TOXIC RETINOPATHY

Untoward visual disturbances were reported with the use of an experimental phenothiazine-piperidinochlorphenothiazine, labeled NP 207.[16-18] The drug has not been released for clinical use. Patients experienced loss of visual acuity and symptoms of impaired dark adaptation. Initial ophthalmoscopic examination indicated hyperemia of the optic disk, retinal edema, and dilation of the retinal vessels. Subsequent examinations revealed retinal pigmentation which originally had fine pepper-like appearance, whereas in more severe cases, irregular circular pigmented areas or a palisading configuration were produced as the spots were noted to coalesce. Several patients, following large daily doses of the drug for at least 4 weeks, showed a fine vitreous haze and flame-shaped hemorrhages. Withdrawal from the drug did not, however, effect the recovery from these ocular complications in all cases.

Burian and Fletcher[19] conducted a detailed study of the retinal function of two patients with severe pigmentary retinopathy as a result of NP 207 and demonstrated profound damage to the rod and cone system. Morrison,[20] previously experienced with the characteristics of ocular toxicity from NP 207, encountered a patient receiving large doses of thioridazine (Mellaril) whose visual symptoms disappeared after the drug was discontinued. He also knew the sequence of at least three other similar reactions with the drug.

Weekley *et al.*[21] reported that in a group of 29 patients receiving thioridazine (Mellaril), 6 had visual disturbances: 2 patients had blurred vision and transient cycloplegia and iridoplegia, and 4 subjects, on high dosage, had severe loss of central visual acuity and later developed pigmentary degeneration of the retina similar to that seen in the patients treated with NP 207. These authors also

cited reports of retinal pigmentary changes that may have been associated with prochloperazine and chlorpromazine therapy.

It is significant that thioridazine is identical to NP 207 except for a thiomethyl group substituted for a chloride at the number 2 position in the phenothiazine derivative. Weekley and coworkers[21] postulated that the piperidine ring present in the side chain of these two phenothiazines at position 10 may be the causative factor of the retinal toxicity and, further, that the degree of toxicity is modified by the substitution in position 2.

BLURRED VISION

On occasion, patients receiving relatively high doses of the phenothiazine tranquilizers have complained of decreased vision. On reduction or cessation of the therapy, this symptom is eliminated. In a recent study,[22] blurred vision was noticed as a side effect of therapy with chlorpromazine (Thorazine), mepazine (Pacatal), perphenazine (Trilafon), prochlorperazine (Compazine), and triflupromazine (Vesprin). There was no mention of ophthalmologic examinations having been performed on these patients.

TOXIC AMBLYOPIA

Johnson[23] observed the case of a 16-year-old boy who developed parkinsonian symptoms after several days of perphenazine (Trilafon) therapy, followed by sudden blindness in 2 days. The results of the ophthalmoscopic examination were negative. The neurologic symptoms and blindness disappeared 1 day after the withdrawal of the drug therapy.

SUMMARY

Ocular complications from the phenothiazine drugs are uncommon but do occur. The true incidence of these side effects will be established only by the detailed study of a large number of patients receiving this medication and by the regular report of any complications. The importance of recognizing the various ocular manifestations of phenothiazine toxicity is that, in most cases, withdrawal or reduction of the dosage of the drug leads to recovery. Ocular complications might also exist which have not yet been appraised. It would be feasible for the ophthalmologist to at least consider the possibility of phenothiazine reaction in any patient who has an unusual or bizarre ophthalmologic condition.

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Clinical Practice

GLAUCOMA

CLINICAL APPLICATION OF GONIOSCOPIC FINDINGS TO EVALUATION OF GLAUCOMA OPERATION

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Gonioscopic examination after operation for glaucoma is useful in determining the prognosis.

Twenty-two eyes with acute inflammatory glaucoma, narrow anterior-chamber angle, and anterior synechias were treated by trephining, Wheeler's operation, or iridectomy. In some instances the first two procedures were followed by Wheeler's operation or Shoji's sclerecto-iridectomy. Usually the result was widening of the angle as viewed through the iridectomy and detachment of the anterior synechias.

Five eyes with chronic inflammatory glaucoma and peripheral or scattered conical synechias were operated upon by trephining or Shoji's sclerecto-iridectomy. In four instances the angle was wider after operation and in one it was closed.

Postoperative gonioscopy showed the size of the iris coloboma was too small in three of the first group of cases, and as a consequence the coefficient of outflow was disturbed, resulting in a poor prognosis. This observation suggests that the dimension of the angle formed by the operation determines the prognosis in cases of glaucoma with close angle before operation.

In simple chronic glaucoma with angles open before operation, formation of anterior synechias as a result of the trephining may also disturb the coefficient of outflow, resulting as in the first group in poor prognosis.

Postoperative examination by means of the gonioscope discloses these postoperative obstructions of the angle, and the diminution of the coefficient of outflow can be shown by tonometry. These disturbances can be corrected, except in cases of malignant glaucoma, by wide iridectomy, cyclodialysis, or Wheeler's operation.

Comment: In the cases described and in the discussion the authors list cases of chronic inflammatory glaucoma with simple glaucoma as having open angles. Obviously these cases are not classified in the same manner we are accustomed to in this country.

The conclusion that the prognosis is related to the presence of peripheral anterior synechias after operation does not take into account the question of the effective filtration resulting from the operation. It is obvious that a completely blocked angle with a filtering trephine or iridencleisis cicatrix may show normal outflow and clinically low or normal tension. The authors emphasize gonioscopy and tonography without relation to the other clinical factors. Glaucoma cases cannot be evaluated except on a total information basis.

SAUL SUGAR

PITFALLS IN GLAUCOMA SURGERY

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Fortunately, many of the pitfalls in glaucoma surgery can be avoided if a thorough examination, careful history-taking, and consultation are carried out before the operation. Failure in glaucoma surgery may be due to the imperfect execution of a procedure. In peripheral iridectomy, a through-and-through opening must be made in the iris. When not even a little aqueous is obtained after application of the scissors, the operator should suspect that only the upper layers of the iris have been incised, and another cut should be made. This mistake, which is often due to overcautiousness, can be prevented by allowing a sufficient amount of iris to prolapse before grasping it with the iris forceps and making the snip. On the other hand, only the portion farthest from the sphincter should be snipped off, as extra-large iridectomies bring about glare and diplopia, making the patient unhappy. Other procedures, such as cyclodialysis and iridencleisis, also require special precautions if they are to be successful.

The rarer complications of glaucoma surgery—choroidal hemorrhage, retinal hemorrhage, and macular edema—are all caused by sudden decompression of the eye, especially in patients with vascular disease. The postoperative pitfalls include uveal reaction, which always develops after surgery involving the iris and the ciliary body; the formation of synechiae (both posterior and peripheral anterior); hyphema; choroidal separation; and prolapse of the iris or the ciliary process into the trephine opening in trephining operations. Occasionally, vitreous may present or even pass through the trephine opening, resulting in failure. When this complication occurs during operation, the procedure may be converted into a sclerectomy with incarceration of the iris (Spaeth).

Lens swelling soon after a glaucoma operation is another complication that sometimes accounts for poor results even after what appears to have been a very neat operation. Delayed reformation of the anterior chamber may have several

causes but is most commonly due to overworking of a fistulizing procedure, especially when there is no shunt between the anterior and the posterior chambers. Fortunately, many shallow anterior chambers reform spontaneously. All that may be necessary is gentle pressure bandaging or bilateral occlusion.

Hypotony is seen more often after a plain cyclodialysis than after a trephining operation. Except for transient macular edema and choroidal congestion and severe astigmatism, hypotony does not seem to be injurious to the eye. It must be remembered, however, that hypotony and phthisis bulbi are not synonymous, although in the latter the eyeball is also soft.

Malignant glaucoma may be prevented by the preoperative use of Diamox and retrobulbar injection with xylocaine and digital pressure during surgery. The management of this complication consists of the administration of Diamox and intracapsular lens extraction followed by intentional rupture of the hyaloid.

But for the danger of cataract formation, glaucoma surgery would be much more popular than it is. A cataract may develop even after a careful operation in which the lens has not been traumatized, or even where the intraocular pressure has not been changed. In such cases, pre-existing lens changes may have been present. For this reason, biomicroscopic examination of the lens should be carried out routinely before operation, and if lens opacities are present, the patient may well be forewarned of the possibility of cataract extraction in the future.

Phthisis bulbi, which is irreversible, is often the result of excessive diathermy application, or of willful destruction of the long posterior ciliary vessels.

A point to be emphasized is that surgical management is often unsuccessful because medical management is suddenly stopped after operation. Many patients would be better off if pilocarpine or even Diamox continued to be administered for a few weeks after operation and then were gradually and cautiously stopped. This is especially true in regard to patients with chronic simple glaucoma that has entered the congestive phase just before operation, but even patients with angle-closure glaucoma should be maintained on miotics for a few days after a successful peripheral iridectomy procedure.

In glaucoma surgery, no less than in well-executed cataract-extractions, favorable results may be secured and the ophthalmic surgeon may experience the joy of seeing a patient relieved of pain and discomfort and the fear of becoming blind.

Comment: A few comments may be helpful to the novice in interpreting some of the many useful suggestions. In describing the use of a strong miotic to prevent peripheral anterior synechias after cyclodialysis, the author states that this keeps the cleft open until epithelialization occurs. More accurate would be substitution of the term endothelialization since there is possibly such an extension of endothelial cells from the trabecular wall. No epithelium is present in the cleft lining.

The statement is made that if it were not for choroidal separation, more ophthalmic surgeons would be doing trephining. Actually, some choroidal separation occurs at least temporarily in all operations where the tension is lowered for any length of time. In itself it is no problem unless it is unduly prolonged and of a degree to shallow the chamber.

When delayed reformation of the anterior chamber is encountered, one must look for leak first. Carbajol's statement that delayed formation is most commonly due to over-working of a fistulizing procedure, especially where there is no shunt between the anterior and posterior chambers, must be challenged. An iris opening or iridectomy is part of every fistulizing procedure and is not a factor. If there is no leak, the shut-off of aqueous secretion which is believed to occur postoperatively for varying periods of time may cause further hypotony which in turn leads to choroidal separation.

Malignant glaucoma, contrary to the author's opinion, cannot be prevented by preoperative use of Diamox, retrobulbar xylocaine, or digital pressure. If it is due to stretching of the zonule and requires removal of the lens, digital pressure may even contribute to it. This condition occurs in both simple glaucoma and angle-closure glaucoma. Removal of the lens is the correct treatment but rupture of the hyaloid is not to follow the extraction except in cases where the chamber does not form following the extraction and where the tension remains elevated.

The author mentions the use of pilocarpine or even Diamox for a few weeks after surgery, especially in patients with chronic simple glaucoma that has entered the congestive phase just before operation. First of all, the idea of a congestive phase with peripheral anterior synechias in chronic simple glaucoma was introduced by this commentator about 20 years ago when he was first studying the classification of glaucoma. A few eyes with advanced simple glaucoma were found to become congested and to show synechias, usually in the absolute glaucoma stage. Since that time, no such cases have been encountered. It is felt that these instances of congestion and synechias in simple glaucoma may all be attributed to a complicating secondary cause. As for the use of pilocarpine or Diamox, it seems wiser to use atropine or homatropine instead in the immediate postoperative period, together with local steroids, at least following fistulizing procedures.

SAUL SUGAR

NEURO-OPHTHALMOLOGY

CONGENITAL INTRAORBITAL ARTERIOVENOUS ANEURYSM

RAMÓN JACAS, ADOLFO LEY, AND DOMINGO CAMPILLO

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J. Neurol. Neurosurg. & Psychiat., 1959, *22:* 330–332

A carotid cavernous fistula has been identified as the most common cause of pulsating exophthalmos. The case presented here is a clinical picture of an intraorbital arteriovenous aneurysm, verified by angiography.

The patient, a woman, 31 years of age, stated that in the last 2 years, without any pathologic antecedent or trauma, she noticed on bending the head a feeling of tension around the left eye. The various ophthalmologists who had seen her

could not find any changes in the visual acuity, fields, or fundi. No abnormalities were found in the x-ray examination of the head, including the orbits and the optic canals. Bilateral carotid angiography was carried out. On the left side a lesion was demonstrated in the posterior-superior part of the orbit. Its appearance was typical of an arteriovenous aneurysm, of which the arterial supply probably came from the lacrimal artery, a branch of the intraorbital portion of the ophthalmic artery. The venous drainage of the lesion was by way of the superior ophthalmic vein.

The commonly accepted etiology of intermittent exophthalmos, as demonstrated in this case, is that of an orbital varicocele, caused by a complete or partial blockage of the venous drainage of the orbit into the jugular vein.

It was the authors' impression that the lesion could be removed surgically. However, there appeared to be a possibility in doing so of damaging the function of the optic or oculomotor nerves, either by direct injury or as a result of the surgical interference with the blood supply of the eye or the orbit. This was discussed with the patient; as she had not had any pain yet and her visual function was well preserved, she decided not to accept the risks of an operation at present unless new circumstances arose.

Comment: This is an excellent article worthy of reporting since it points out the various etiologic causes for pulsating exophthalmos and the relationship of this clinical diagnosis to intraorbital and intracranial arteriovenous aneurysms.

THOMAS R. HEDGES, JR.

OCULAR PALSY IN TEMPORAL ARTERITIS

PART II

C. MILLER FISHER

Boston, Massachusetts

Minnesota Med., 1959, *42:* 1430–1437

No comprehensive account of the more general central nervous system manifestations of temporal arteritis, which, when added to the visual and ocular signs, may serve to complete the neurologic part of the clinical picture, can be found in the literature. Consequently, the author decided to review the neurologic features of each of the several arteritides (periarteritis nodosa, granulomatous angiitis, and the rest), for the purpose of demonstrating the relationship, if any, of temporal arteritis to the other arteritides and at the same time pointing out the ways in which it differs from them clinically and pathologically.

The cause of each of the arteritides remains obscure, although they are com-

monly regarded as manifestations of an allergic process. The discovery of a common thread of etiology running through the various types would be important, but on the basis of clinical and pathologic features a unitary concept cannot now be justifiably formulated. Omitting the cranial arteritides, whose etiology is more or less understood, the arteritides may be listed as follows: (1) periarteritis nodosa, (2) allergic granulomatous angiitis with asthma and eosinophilia (granulomatous angiitis), (3) hypersensitivity angiitis, (4) Wegener's granulomatosis, (5) unclassified periarteritis, (6) temporal arteritis, (7) idiopathic arteritis of the aortic arch and its branches, (8) rheumatic arteritis, and (9) thromboangiitis obliterans.

Although in temporal arteritis many other large arteries of the body are involved, the present terminology is advantageous because of precedence and custom and because it connotes the approximate site of the most important clinical features of the illness, namely, headache and blindness. The fundamental lesion is a mildly destructive inflammatory process involving the temporal and various other large arteries; lymphocytes, plasma cells, macrophages, and polymorphonuclear leukocytes are found throughout the thickened vascular wall but especially in the media, and giant cells are characteristically present. Subintimal proliferation of connective tissue narrows the lumen and thrombosis is occasionally added. Vascular nodules and aneurysms are usually not found. Many external cranial vessels besides the temporal and occipital arteries are affected. Allergy and hypersensitivity play no overt part in the etiology of the disease. Almost all the patients are elderly.

Unfortunately, in many of the reported cases, the neurologic information is so brief that no clear picture of the patient's condition can be obtained. Excluding visual and oculomotor disturbances resulting from involvement of the optic nerve, which have been reviewed on several occasions by other authors, the assembled reports seem to show that involvement of the central nervous system in temporal arteritis is not uncommon. Delirium and confusion are mentioned most often, but whether these symptoms are produced by involvement of the brain by the arteritis or are merely the "non-specific" effect of a systemic disorder in elderly patients is not clear. Hemiplegia as a result of carotid occlusion is the next most frequent finding, followed closely by signs of involvement of the brain stem or the eighth nerve, viz., tinnitus, dizziness, and deafness, manifestations of temporal arteritis which deserve more attention than they have heretofore received.

More than one of these various neurologic manifestations of temporal arteritis may, of course, appear in a single patient, as illustrated by the first case of temporal arteritis with cerebral symptoms encountered at the Massachusetts General Hospital. The patient, a 76-year-old man, had severe headache in the occipital area for about three weeks beginning in late October, 1957. For several weeks previously there had been malaise, anorexia, and loss of weight. The headache, which at no time extended anterior to the ears, stopped about November 19. Six days later the patient became totally blind in the left eye, overnight. Three days after this, vision in the right eye was noted to be poor. On Meticorten ther-

apy the patient felt better generally, but vision did not improve. Meticorten was discontinued after about five weeks (January 7, 1958) and the patient's course was uneventful until February 27, when his wife reported that his right hand had been transiently limp twice in one day. The patient stated that on three occasions in the previous 4 days there had been brief spells in which his right hand shook. On examination, he was found to be disoriented for time and place; he did not recognize his physician, made a few mistakes in naming objects, was quite unable to do simple arithmetic, and had a Babinski sign on the right side. Meticorten therapy was reinstituted, but in spite of large doses (up to 150 mg. each day) the patient's course during the following 5 weeks was punctuated by episodes of weakness and confusion whose nature was not established with certainty. On April 6, he was discharged on anticonvulsant medication. He had no further spells, but 5 days later occlusion of the left femoral artery occurred and the foot became gangrenous. He remained confused and his condition gradually deteriorated until, 8 weeks after his discharge, he died. No postmortem examination was made and the role, if any, of atherosclerosis in the production of the complications was never determined.

Many of the features of the patient's attacks suggested epileptic seizures, but since it was reliably reported that sometimes paralysis of limbs had occurred without any preceding convulsive activity, transient ischemic attacks were also a good possibility. If the vascular occlusion of the lower extremity was caused by arteritis, it represents a most rare event. In one of Fragenheim's (1951) cases, the patient had gangrene in one lower extremity and femoral arteritis was found in the amputated limb, but there was little or no evidence of a generalized arteritis.

From the material presented, it is evident that a more accurate and detailed account of the neurologic manifestations of temporal arteritis is needed.

Comment: No comment because author's own comment very good.

BERTHA KLIEN

OCULAR PALSY IN TEMPORAL ARTERITIS

PART III: NEUROLOGIC MANIFESTATIONS OF THE ARTERITIDES OTHER THAN TEMPORAL ARTERITIS

C. MILLER FISHER

Boston, Massachusetts

Minnesota Med., 1959, *42:* 1617–1629

Involvement of the nervous system in periarteritis nodosa and closely related types of arteritic disease takes quite a different form from that encountered in

idiopathic arteritis of the aortic arch and its branches (Takayasu's disease). In none of them is there a close resemblance to temporal arteritis.

In periarteritis nodosa by far the commonest site of involvement of the nervous system is the peripheral nerves, with the production usually of a multiple asymmetric neuropathy (mononeuritis multiplex) evoked by ischemic necrosis of the nerve bundles. The cranial nerves may be affected also, with the production of an extraocular palsy, facial palsy, vertigo, and other disturbances.

Symptoms and signs of involvement of the central nervous system are not uncommon in periarteritis nodosa and take a variety of forms reflecting the nature of the lesions (infarction, hypertensive hemorrhage, rupture of aneurysm, cerebral edema, and so on) and their haphazard distribution. Convulsions, hemiplegia, disorientation, and confusion are commonest. Occasionally, the picture of subarachnoid hemorrhage or meningitis may be prominent. Chorea, blindness, ptosis, ocular palsies, transient attacks of cerebral ischemia, diabetes insipidus, and an encephalitis-like state have been reported.

On the whole, it may be said that the cerebral arteries are apparently not commonly affected in periarteritis nodosa; when they are, the clinical picture reflects the widespread distribution of multiple small lesions, rather than a gross focal neurologic deficit as in most cases of stroke associated with atherosclerotic vascular disease. Occlusion of small arteries results in tiny areas of ischemic necrosis and any level of the neuraxis, cerebrum, brain stem or spinal cord may be involved. Hemorrhage from inflamed vessels appears to be extremely rare. Systemic disease was evident in all but a few of the reported cases summarized in this paper. It should be emphasized that in only one case was there involvement of the temporal artery or the larger vessels arising from the arch of the aorta, and in that case the lesion did not resemble temporal arteritis.

The fact that clinically there is a cerebral form of granulomatous angiitis in which the neurologic features of the disease predominate over the manifestations of involvement of other organs is becoming increasingly clear. Pathologically, the cerebral form is usually part of a generalized process and only in one case (Cabot, 1955) were the lesions proved to be limited almost exclusively to the central nervous system. In the other cases in which postmortem examination was complete, a wide-spread distribution of the arteritis was the rule. Possibly granulomatous angiitis has a special predilection for the vessels of the nervous system despite Rose and Spencer's estimate of the incidence at only 3 per cent.

With little exception, the manifestations evoked by idiopathic arteritis of the aortic arch and its branches (Takayasu's disease) have been the result of occlusion of the large vessels arising from the arch of the aorta and the production of ischemia distally. Although the intracranial vessels are not directly involved, neurologic signs due to cerebral ischemia are prominent. The clinical picture (the aortic arch syndrome) is now well known and includes absence of pulsations in the carotid and temporal arteries and the arteries of the upper extremities, diminished or absent blood pressure in the arms, sometimes hypertension in the lower half of the body, postural syncope, a tendency to hang the head forward, convulsions, dizziness, a predisposition to tussive syncope, cerebral claudication,

hemiparesis or numbness, aphasia, intellectual deterioration, loss of vision (transient or permanent monocular blindness), optic atrophy, and other ocular and general disturbances. The duration of the symptomatic part of the illness is usually several years and the process probably exists silently for some time before manifesting itself. The other causes of the aortic arch syndrome must always be excluded—atherosclerosis with thrombosis, syphilis, tuberculosis, and healed aortic dissection.

In no case of Takayasu's disease has temporal arteritis been evident, nor has temporal arteritis been reported as a cause of the aortic arch syndrome. The data presented in this brief review provide sufficient justification for keeping the two diseases separate at the present time. In the recognition of Takayasu's disease, it is important not to overlook cases in which the syndrome is merely partial, with only one, two, or three of the main brachiocephalic trunks showing obstruction.

Comment: In this article the author discusses the neurologic manifestations of periarteritis nodosa, allergic granulomatous angiitis, and idiopathic arteritis of the aortic arch and its branches. The latter disorder is often referred to as Takayasu's disease or pulseless disease.

From the standpoint of the ophthalmologist, the manifestations of periarteritis nodosa in the eye and orbit are very diverse. Several observers have estimated the frequency of ocular involvement to be 10 per cent to 20 per cent of the cases of periarteritis nodosa. However, these statistics are not based on a large series of cases. There is a paucity of autopsy examinations of the eyes and orbits in people who have died from the generalized disease. In many case reports an exact explanation is not included as to why the patient had blurred vision. All of these factors contribute to our incomplete knowledge as to the true frequency of ocular involvement in this collagen disorder.

It does seem that almost all tissues of the eye, even the relatively avascular tissues, may participate in the disease. The ocular tissues either may be the site of a localized periarteritis or they may reflect, in the form of retinopathy or edema, the involvement of some other organ such as the kidney. In my own practice I do not know of any ophthalmic clue that is typical of periarteritis nodosa. However, during the course of ophthalmic consultations, particularly on patients hospitalized on other medical services, I am quite suspicious that the answer to an otherwise puzzling diagnostic problem might be periarteritis nodosa if I note an unusual ocular disorder associated with an elevated sedimentation rate in a middle age or young adult individual who also has bouts of fever.

The disorder, allergic granulomatous angiitis, is even less well known than the preceding disease as far as ocular complications are concerned. It is only in the last decade that pathologists have recognized this disorder as a distinct ocular involvement in this disease. The reader is referred to Cury *et al.*, A.M.A. Arch. Ophth., *55:* 261, 1956.

The pattern of ocular involvement in the third disorder, idiopathic arteritis of the aortic arch and its branches, is better understood than the preceding two diseases. In this third type of arteritis the ocular symptoms are directly related to a slowing down of the blood flow through the carotid arteries. In the initial stages of the arteritis the patient will experience transient episodes of visual blurring. These episodes of visual loss may be brought on by a sudden change in posture from the reclining to the upright position. At this stage, ophthalmodynamometry will reveal the reduced pressures in the retinal arteries. As the disease progresses, optic atrophy may appear and a peripapillary

arteriovenous anastomoses will be visible by ophthalmoscopy. In the late stages of the disorder neovascularization of the periphery of the iris and development of cataract will occur. All of these ocular changes are the result of a progressively increasing local anoxia.

There are many variants of the aortic arch syndrome, and the symptomatology will depend on the number and location of the arteries involved. The terms "pulseless disease" and "Takayasu's disease" probably should be applied only to those cases occurring in individuals (usually women) less than 40 years of age who show the more advanced stages of the ocular complications.

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CHIASMAL DISEASE

ALAN J. MOONEY

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J. Irish Med. Assoc., 1959, *45:* 47–50

Steady visual failure unaccounted for by local ocular disease, with or without disk failure, should demand immediate detailed perimetry. Eight cases are described to show the value of this test both as a localizing guide and as a means of assessing the progress of the case after either operation or radiotherapy.

In case 1 an upper bitemporal hemianopia suggested chiasmal involvement, and a macular loss on the left side pointed toward a lesion lifting up the left optic nerve. The perimetry follow-up underlined the initial success of the operation and also provided evidence of recurrence.

In case 2 the perimetry pinpointed the lesion, which could have been either an aneurysm or neoplasm. Angiography excluded the former.

The association of enlargement of the sella, normal disks and bitemporal hemianopia in case 3 suggested a retrochiasmal tumor unsuitable for surgery.

Case 4 showed disk pallor with unequal bitemporal field defects, a finding usually associated with prechiasmal lesion (in this case a cystic tumor) dislocating the optic nerves laterally.

Case 5 had perimetric findings suggestive of pituitary tumor. Angiography, which is a routine procedure in all the author's suspected chiasmal lesions, showed an internal carotid aneurysm. This case brings out the limitations of perimetry with respect to the nature of the lesion.

Case 6 showed the chiasmal syndrome, described by Cushing, of chiasmal optic atrophy with bitemporal field defects showing an essentially normal sella turcica.

In case 7 complete visual recovery followed the operation for arachnoiditis after conservative treatment had failed.

In case 8, the ophthalmic examination gave a fairly accurate estimate of the position of the interference with the visual pathway, but not its nature—a distended third ventricle, one of the less common causes of chiasmal disease.

From experience, we have formed certain impressions with regard to chiasmal lesions:

1. Where symmetrical bitemporal hemianopia is present with normal disks, the tumor is mainly retrochiasmal and more suitable for radiotherapy than surgery.
2. Where asymmetrical nonscomatous bitemporal field defects are present with some degree of disk pallor, some of the tumor is prechiasmal, spreading upwards between the optic nerves and displacing them laterally.
3. Where there is incomplete temporal hemianopia on one side and temporal hemianopia with macular loss on the other, the swelling is probably subchiasmal, elevating the nerve on the scomatous side.

In chiasmal lesions where the patient's initial symptoms are visual, the ophthalmologist should be the first to suggest the site of the lesion. He may even go further by suggesting a certain course of treatment, whether it be operative or radiologic. Beyond this he should not be prepared to go, unaided.

Comment: The author presents a varied and instructive series of chiasmal cases. He stresses the view that any progressive visual failure not explained by ocular disease should lead to immediate quantitative perimetry whether there is any visible pallor of the disks or not. It is interesting to note in reviewing his cases that 6 of the 8 also had an entering complaint of *monocular* visual loss. This was true of pituitary adenoma, craniopharyngioma, aneurysm, suprasellar meningioma and dilated third ventricle. One of his patients demonstrated the field defect in a chromophobe adenoma by the way in which the visual chart was read—missing letters to the left with the left eye, and to the right with the right eye. This clue can often be helpful. One should note the author's statement that arteriography is *routine* in his chiasmal lesions. He believes that enlargement of the sella together with normal disks and bitemporal hemianopsia suggests a retrochiasmal lesion unsuitable for surgery; however, in the patient presented to demonstrate this point of view a normal angiogram was obtained. This would indicate a rather small lesion. In contrast, where disk pallor is present with unequal bitemporal field defects, the lesion is usually prechiasmal and displaces the optic nerves laterally. In addition, this patient may demonstrate macular involvement in the visual field of the more involved eye as well. The macular loss indicates elevation of the prechiasmal optic nerve.

The necessity of close liaison between the neurosurgeon and the ophthalmologist in such patients is stressed by the author, and I agree completely. Only in this way can the patient's best interests be served.

JOHN WOODWORTH HENDERSON
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THE EFFECTS OF CAROTID CAVERNOUS FISTULA UPON THE EYE

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New Zealand J. M. (Suppl.), 1959, *11:* 19–22

Small leaks from the carotid artery into the cavernous sinus are uncommon. The author reports 5 cases, 3 of which followed trauma and 2 developed spontaneously, probably due to rupture of an aneurysm into the sinus.

The leak into the sinus increases pressure in the veins from the brain and orbit which drain the sinus. The resultant venous congestion seems to cause no symptoms in the brain, but may cause variable symptoms in the orbit. The degree of orbital congestion apparently depends on the presence or size of a second route of orbital venous drainage, that from the pterygo-maxillary fissure. In severe cases, orbital congestion may suggest cellulitis, while milder cases may have few if any symptoms. Some have slightly engorged conjunctiva, proptosis, and retinal vein engorgement which either change little over a long period of time, or lead to glaucoma within 2 years.

Ten per cent are said to recover spontaneously, as did 2 of our cases. Surgical treatment may be necessary in the others. The usual method is carotid ligation either in the neck alone or in the neck and also within the cranium. The more severe cases should be operated upon at once if they tolerate tests of carotid compression. Since we do not know which of the milder cases may recover spontaneously or which may later have glaucoma, the decision to operate in these cases is less clear.

Five case histories are reported. The first patient had gross exophthalmos and corneal ulceration, but recovered completely after ligation of the common carotid artery. The second could not tolerate any form of carotid artery compression and has continued to function with head noise and a blood-shot eye. The third developed acute glaucoma 2 years after unsuccessful ligation of the common and internal carotid arteries in the neck, and intracranial ligation also failed to relieve the eye condition. The other 2 patients recovered without treatment.

We conclude that operation is urgent only in cases with gross orbital edema. The others can probably be observed for a few months. If the condition does not improve within a year, the ligation should probably be carried out in the neck, and if this is not adequate, intracranial ligation can be done after 2 weeks.

(*See editorial comment following next paper.*)

CAROTID CAVERNOUS FISTULAS: DIAGNOSIS AND SURGICAL MANAGEMENT

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Am. Surgeon, 1958, *24:* 839–843

A carotid cavernous fistula may follow a head injury, even a trivial one, or it may be spontaneous in onset. When this condition is recognized soon after its onset and promptly treated, the results are gratifying. If the condition is not diagnosed and treated, it is, at best, distressing to the patient. Pounding headache—usually of a pulsating type—chemosis, diminished visual acuity, and paralysis of one or more of the nerves serving the ocular muscles are the principal clinical features.

Angiographic demonstration of the blood flow pattern at the cavernous sinus shows that there are two types of fistulas—those in which all blood from the internal carotid is diverted into the cavernous sinus and those in which a significant supply of blood still reaches the brain despite the fistula. All patients with carotid cavernous fistulas should be subjected to carotid angiography, at least on the involved side, and preferably bilaterally to determine the type of diversion and most suitable operative procedure.

Eight of the 14 patients discussed in this paper were treated by primary cervical internal carotid artery ligation with subsequent intracranial carotid occlusion. Four of these patients were in the total diversion group and 4 had partial diversion of carotid flow. In none of these 8 patients did hemiplegia develop, nor were there any deaths. The symptoms caused by the fistula itself were relieved in all patients, although one had a bruit audible to the examiner only.

In the other 6 patients the intracranial portion of the internal carotid was occluded at a point between the ophthalmic artery and the posterior communicating artery. Then, at the same operative session, the cervical portion of the internal carotid was doubly ligated and sectioned. During this procedure the brain is at no time deprived of more blood than it has been losing into the fistula. In this group also in no patient did hemiplegia develop nor were there any deaths. One patient had persistent abducens nerve weakness; also one patient in this group has a bruit which can be heard only by the examiner.

The existence of a bruit, despite apparent isolation of the fistula from the arterial circulation, demands an explanation. There are several small arteries arising from each internal carotid artery as it passes through the cavernous sinus. The branches enter the pituitary fossa and anastomose within it. If correction of a carotid cavernous fistula is not accomplished soon after its onset, it is reasonable to suppose that these anastomosing vessels could develop a circulation great enough to maintain the fistula. If this blood flow through the fistula

causes continued signs and symptoms, introduction of muscle into the carotid artery might be necessary.

Comment: These two papers add further information to our concepts of management of these fascinating problem cases. The early patient may present a picture to the ophthalmologist which may suggest inflammatory orbital disease with associated vascular congestion, but the history of head injury in the majority and the presence of a bruit remind us that a stethescope should always be used in the differential diagnosis of orbital disease. Contrary to many authors, Robertson feels that observation is justified in mild cases. However, those who advocate early surgery feel that orbital changes are less likely to reverse after long delay. The editor, and his neurosurgical colleague Dr. Richard C. Schneider (Am. J. Ophth., *48:* 585–597, 1959) recommend aggressive attack on such cases, believing that the final regression of measureable proptosis is best with surgery. Wherever possible, based on the sufficiency of the carotid arteries, early cervical internal carotid ligation combined with intracranial clipping of the internal carotid and ophthalmic arteries should be performed. Hayes follows a similar procedure where possible except that he does the intracranial ligations before the cervical closure.

The danger of glaucoma in the involved eye is noted by Robertson as a late complication. This was also found to be an early complication in the editor's series of cases, occurring in 41 per cent of 17 patients. The secondary glaucoma was of two general types. In the first, orbital venous back-pressure raises the intraocular tension. This usually responds to surgery of the primary vascular orbital disease or to miotics. The second type usually follows prolonged orbital involvement and unsuccessful vascular surgery and is probably secondary to both venous and arterial retinal occlusion, since it is also associated with a complicated cataract.

Ocular muscle palsy is a frequent part of this disease, either by direct pressure on nerve trunks by the fistula, or secondary to the original skull fracture leading to the arteriovenous communication. Hayes notes oculomotor involvement of 7 of 14 patients, and sixth nerve paralysis of 8. In the editor's series of 17 patients, 7 had oculomotor palsy, 6 had trochlear involvement, and 10 showed lateral rectus paralysis. In 3 patients the paralyses were bilateral, and in all these the etiology was presumed to be the basilar skull fracture.

JOHN WOODWORTH HENDERSON
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MUSCLES

MYOPATHY IN CUSHING'S SYNDROME

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J. Neurol. Neurosurg. & Psychiat., 1959, *22:* 314–319

No systematic investigation has been reported on muscular weakness in Cushing's syndrome, although it is a well known feature. Motor function was studied in 6 patients and muscle biopsy in 4. Clinically 5 patients showed weakness of pelvic girdle and thigh muscles and two also of shoulder girdle and dorsiflexion of feet. In 2, weakness was the first symptom and in 3 it appeared several years later. Electromyographically 5 showed general reduction in the size and duration of motor unit potentials and increased proportion of polyphasic potentials. Electromyographic changes were seen also in muscles with no clinical paresis. Histologically muscle fibers to small extent were replaced by connective tissue and fat. Majority of fibers were thin but normal, some hypertrophic and others degenerated lying singly or in groups with rounded contour, hyalinized appearance and obscured striations. Some sarcolemmal nuclei were dark, small, elongated, increased in number and arranged in longitudinal rows with occasional nuclei migrated centrally.

Cause of muscular weakness probably lies in the muscle itself. It may be a metabolic disorder which decreases the contractile power of individual muscle fibers or a numerical reduction of functioning fibers in motor units. Electromyographic pattern was characteristic of reduced functional fiber disorders. Such changes are not specific as they may occur in reversible functional disturbances or through less morphologic muscle changes. Histologically muscle fibers showed pronounced degeneration. Consequently, in Cushing's syndrome it is a question of true myopathy. Thus, it resembles thyrotoxic myopathy where severe muscular weakness is not necessarily associated with pronounced morphologic changes. Muscular weakness due to electrolyte disturbance seems unlikely as paresis persisted unchanged over long periods and muscle power remained unimproved despite regression of other symptoms with treatment. Of course biopsy specimens might not have been representative of affected muscle and routine histological techniques inadequate.

Myopathy in Cushing's syndrome may be related to increased corticoid productions. Reversible muscle changes have been induced in animals with cortisone and ACTH. In patients changes were invariable clinically and on biopsy and less pronounced than in experimental cortisone myopathy. Patients were estimated to be producing 2 mg. per kg. of body weight of corticoids (much

less compared to that administered experimentally) and were exposed to effect of increased corticoid production for years. Prolonged cortisone medication is known to lead to severe muscular weakness and it is possible that it is due to myopathy of the same type as in Cushing's syndrome.

Comment: The authors deserve our commendation for reporting the first detailed and systematic study of the muscular weakness in Cushing's syndrome. The clinical, electromyographic and histologic evidence presented by them in favor of this muscular weakness being a true myopathy is overwhelming and the reviewer is in whole-hearted agreement with their interpretation. Experimental evidence quoted seems to correlate well with the clinical findings. It would have been interesting if the authors would have obtained biopsy specimens from various muscles and applied specialized staining techniques (C. Coers, and A. L. Woolf: *The Innervation of Muscle: A Biopsy Study*. Charles C Thomas, Springfield, Ill., 1959). Let us hope they do so in future. Further studies are needed by other workers on this aspect of Cushing's syndrome.

We learn that muscular weakness may be the first presenting symptom in Cushing's syndrome, a point which the clinician would be well advised to keep in the back of his mind.

NARENDRA KRISHNA

DIAGNOSTIC TESTS

SARCOIDOSIS AND HYPERPARATHYROIDISM WITH HYPERCALCEMIA: SPECIAL USEFULNESS OF THE CORTISONE TEST

JANICE M. BURR, JOHN J. FARRELL, AND A. GORMAN HILLS

Miami, Florida

New England J. M., 1959, *261:* 1271–1275

Recent studies show that in certain conditions cortisone regularly and promptly reverses hypercalcemia and hypercalciuria with excessive proportional absorption of dietary calcium and elevated renal calcium clearance. This response does not occur when these symptoms are caused by parathyroidism. The cortisone test may therefore help to diagnose the cause of hypercalcemia when it is otherwise difficult to establish. It may also be useful in the unusual situation when two conditions, both of which may cause hypercalcemia, coexist.

A case is reported, apparently the third of its kind, of a patient with co-existent sarcoidosis and hyperparathyroidism. Symptoms first suggested sarcoidosis as the probable diagnosis, but since hypercalcemia did not respond to cortisone, hyperparathyroidism was suspected. Neck exploration disclosed a parathyroid

adenoma, which was removed without complications, and followed by return of calcium levels to normal.

When the patient had recovered, her abdomen was explored because of a large mass in the upper left quadrant. This proved to be the spleen, which, with the appendix and two lymph nodes from the gastrosplenic region, was removed, and a liver biopsy was taken. Microscopic examination showed sarcoidosis. After a period of clinical observation and treatment, including a brief second episode of hypercalcemia, the patient was well.

While cancer and Hodgkins' disease do not respond clearly to the cortisone test and other exceptions have been noted, apparently a typical positive response to cortisone excludes parathyroidism as a cause of hypercalcemia. On the other hand, if the response is negative, the result is consistent with a diagnosis of hyperparathyroidism, though it is not diagnostic. Negative results also exclude vitamin D intoxication, infantile hypercalcemia, and sarcoidosis. Probably, though not certainly, other glucocortical compounds can be substituted for cortisone in the test. There is also some evidence that patients with sarcoidosis and infantile hypercalcemia are abnormally sensitive to the effect of vitamin D on calcium absorption and serum concentration.

Comment: This article is of value to ophthalmology since we are often concerned both with the diagnosis of sarcoidosis and hyperthyroidism with hypercalcemia. The administration of cortisone acetate in patients with elevated serum calcium concentrations accompanying sarcoidosis produces a regular and prompt lowering to normal. This does not occur in hyperparathyroidism as a cause of hypercalcemia and failure of serum calcium to respond to the cortisone is again consistent with, although by no means diagnostic of hyperparathyroidism.

THOMAS R. HEDGES, JR.

PUPIL

HORNER'S SYNDROME: AN ANALYSIS OF 216 CASES

C. L. GILES AND J. W. HENDERSON

Am. J. Ophth., 1958, *46:* 289–296

Found coded as Horner's syndrome were 216 cases in the University Hospital records (Michigan) of the years 1936–1957. It is possible that additional, uncoded cases were seen during this period. Furthermore, the selection of cases in a large diagnostic center does not necessarily reflect the incidence of a condition in the population at large, because the cases are preselected by the very fact of referral.

The cases were analyzed with respect to location and etiology of the lesion, and age of the patient.

The most common site of interruption of the sympathetic path to the eye was the sympathetic trunk and the postganglionic fibers before they course intracranially. The lower cervical and upper thoracic roots of the spinal cord were affected less than half as often as the sympathetic trunk, while the brain stem, spinal cord and postganglionic fibers in their intracranial course were only rarely affected.

Neoplasia, far more often malignant than benign, was the most frequent etiologic condition. Bronchogenic and metastatic carcinoma were the most common malignant, neurofibroma and thyroid adenoma the most frequent benign tumors. Surgical procedures, trauma (birth trauma and accidents) and vascular conditions followed in the order of frequency.

When the lesion was situated in the peripheral sympathetic chain, tumors were the predominant cause, while trauma and vascular conditions were more frequently encountered in cases with lesions in the brain stem, the spinal cord, or the spinal roots.

Horner's syndrome was less prevalent in the young than in the older age groups. In the group from birth to 20 years of age, trauma accounted for the majority of cases, while in the older groups, tumors were the most frequent cause of the syndrome.

In view of the frequently serious nature of the lesions involved in the production of Horner's syndrome, it is necessary to investigate each case thoroughly. Such investigations should include detailed reporting of the patient's history, especially of all operative procedures, head or neck trauma, age and onset of condition. Ophthalmologic, neurologic and general physical examinations, x-rays, including stereoscopic and lateral views of the chest, lateral views of the cervical and upper thoracic spine, and routine skull films, pharmacologic tests of the pupil and sweating tests are advised.

Comment: This interesting paper emphasizes that we have little reason to be complacent upon finding a pupillary Horner's syndrome. Depending upon its location and nature, the causative condition may be benign or serious, stationary or progressive. No case should therefore be dismissed with a diagnosis of "peripheral Horner" without most careful investigation. The paper renders a valuable service by stressing these points.

The authors found only one case with damage to the postganglionic sympathetic fibers in their intracranial course (after Herpes Zoster ophthalmicus). In our experience, intracranial postganglionic lesions have been more common. A probable explanation of this difference in findings may be contained in the fact that intracranial postganglionic sympathetic lesions are often combined with damage to the parasympathetic innervation of the same eye. The postganglionic fibers which join the Gasserian ganglion and reach the orbit with the ophthalmic branch of the fifth nerve run in rather close proximity to the efferent oculomotor fibers. When a lesion involves the two nerves, the effects of the sympathetic lesion (miosis) and of the parasympathetic lesion (mydriasis) often tend to counteract one another, and the pupil may appear fairly normal to the naked eye, while pupillographic records may reveal the double—sympathetic-parasympathetic—involvement. In addition, the usually more complex cases with intracranial interruption of the

sympathetic fibers are less likely to be coded as "Horner's syndrome" in hospital records.

Two small corrections should be added to the anatomical chapter of the paper.

1. According to the bulk of careful experiments reported in the literature, the spinal cord is unlikely to contain pupillary elements below the level of T2 (T4 in the authors' diagram).

2. The authors assume an entirely uncrossed neuron for pupillary dilation from the posterior hypothalamus to the center of Budge in the cervico-thoracic spinal cord. Such a path has not been established. The literature is ambivalent about this subject. In our own clinical and experimental work, we found that pupillary inequality may, but must not, accompany diencephalic lesions, while unilateral diencephalic stimulation (in cats and monkeys) usually resulted in bilateral pupillary responses.

OTTO LOWENSTEIN

SUI DISTURBI PUPILLARI NELLE PARALISI ISOLATE DEL PICCOLO OBLIQUO (PUPILLARY DISTURBANCES IN ISOLATED PARALYSIS OF THE INFERIOR OBLIQUE MUSCLE)

G. SCASSELLATI SFORZOLINI

Riv. oto-neuro-oftal., 1957, *32:* 582–589

The author describes the case of a 34-year-old railway worker who was struck by a piece of iron in the inferior-temporal region of the left orbit. He showed isolated paralysis of the inferior oblique without pupillary involvement. The condition healed spontaneously.

Based on this case, the author reviews the literature. He disagrees with the widely accepted opinion that isolated paralysis of the inferior oblique is usually accompanied by damage to the parasympathetic innervation of the eye. Such general statements in the literature are not supported by clinical data. Actually, pupillary involvement only rarely accompanies isolated paralysis of the inferior oblique because the common path of the pupillary and the inferior oblique fibers is short and deeply buried in the orbit. In contrast, the third nerve fiber to the inferior oblique muscle, peripheral to the point of exit of the autonomic fibers in the short root of the ciliary ganglion, is long and is exposed to trauma near the floor of the orbit and the bony margin of the orbit.

Comment: It is a pleasure to follow the author's well-organized discussion. The anatomical relations and the clinical case are clearly presented and well illustrated. We would agree that it is difficult to imagine frequent coincidence of paralysis of the intrinsic ocular muscles and of isolated paralysis of the inferior oblique. The inferior oblique branch of the third nerve, from its origin to the point of emergence of the autonomic fibers, is not only short and deeply buried near the apex of the orbit, but in addition, it runs in

close proximity to the rest of the orbital nerves. The frequent occurrence of isolated damage to this part of the nerve is thus not probable.

OTTO LOWENSTEIN

RETINA

CASES OF DIABETES OF LONG DURATION

H. C. HAGEDORN, M.D.

New England J. Med., 1959, *261:* 442

A follow-up study of the first 8 patients treated in Denmark with insulin for severe diabetes mellitus reports 5 still alive and 3 dead in 1959. Two of the deceased died after 22 and 28 years of treatment. Of the survivors, 4 have normal vision, one with slight cataract, and the 5th significant retinopathy. Detailed data are given in Table 1.

TABLE 1

Data in the First 8 Danish Diabetic Patients Treated with Insulin

Case No.	Sex	Occupation	Year of Birth	Year Diabetes Demonstrated	Late Diabetic Complications		Other Complications	Present State
					Eyes	Kidneys		
1	M	Dentist	1883	1917	—	—	Patient died of circulatory insufficiency on the day after institution of insulin treatment	Patient died in 1923
2	F	Housewife	1912	1918	Normal vision; ophthalmoscopy showed single microaneurysm in right fundus.	No proteinuria (blood pressure 135/80)	None	Normal working capacity; 2 children.
3	M	Painter	1902	1921	Normal vision; ophthalmoscopy gave normal findings.	No proteinuria (blood pressure 135/75)	Coronary occlusion in 1953	Normal working capacity; no complaints.
4	M	Manager	1887	1916	Operation in 1933 for cataract; normal vision with glasses; ophthalmoscopy gave no sign of retinopathy.	No proteinuria (blood pressure 130/70)	Operation in 1943 for hypertrophy of prostate gland	Patient still active leader of his firm; no complaints.

TABLE 1—*Continued*

Case No.	Sex	Occupation	Year of Birth	Year Diabetes Demonstrated	Late Diabetic Complications		Other Complications	Present State
					Eyes	Kidneys		
5	M	Employee in factory	1906	1918	Slight cataract in both eyes; ophthalmoscopy gave normal findings in right eye, with few microaneurysms & single hemorrhage in left eye; vision good.	No proteinuria (blood pressure 115/75)	Coronary occlusion in 1958	Patient convalescent after heart attack & is doing half - day work; is able to ride on motorbicycle
6	F	Housewife	1911	1918	Patient living abroad & has retinopathy, with visual power reduced to 6/36	—	—	Patient leading active life abroad & able to take care of 2 adopted children
7	F	Housewife	1871	1921	—	—	Patient died in 1945 of cancer of stomach	Patient died in 1945
8	M	Mechanic	1899	1922	In 1949 normal vision & ophthalmoscopy gave normal findings; in 1951 slight retinopathy.	Proteinuria since 1935 (blood pressure 105/70 in 1948 & 170/90 - 145/80 in 1951)	In 1935 tonsillitis followed by thrombophlebitis of jugular vein & hemorrhagic nephritis; patient died in Nov. 1951, of coronary occlusion.	Patient died in 1951

Comment: In this report 5 diabetic patients are described who have survived an average of 41 years of diabetes. Most interesting is the absence of retinopathy in 2 patients after 38 and 43 years of diabetes, and the finding of only minimal retinopathy in 2 others of similar duration. The author attributes these results to rigid dietary treatment in addition to insulin.

BERNARD BECKER

DIABETES MELLITUS AND ADDISON'S DISEASE

A REPORT ON EIGHT PATIENTS AND A REVIEW OF 55 CASES IN THE LITERATURE

D. W. BEAVEN, DON H. NELSON, ALBERT E. RENOLD, AND GEORGE W. THORN

New England J. Med., 1959, *261:* 443

Since 1942, 8 patients with both Addison's disease and diabetes mellitus have been seen at Peter Bent Brigham Hospital; 6 of these have been previously un-

reported; all 8 are reviewed in detail. Review of the literature reveals that 55 cases have been previously reported that can be identified with reasonable certainty. The 63 cases are compared by dividing them into 3 groups: (1) Addison's disease preceding diabetes mellitus, (2) diabetes mellitus preceding Addison's disease, and (3) those cases with simultaneous onset.

Group 1 consists of 21 patients, 13 male and 8 female. Addison's disease appeared on an average 3 years before the onset of diabetes. Five of the patients had diabetic coma and precoma. A higher dosage of insulin was required in cortisone-treated patients. Attacks of hypoglycemia were reported in all but 2 of the 21 patients, with death attributed to it in 3 of the 9 known deceased patients. Two died from unknown causes, and 3 from infection. Calcifications and tuberculosis were noted rarely.

In Group 2, (37 cases, 19 male, 18 female) 14 cases diagnosed as Addison's disease had histories of diabetic coma or precoma, but the incidence of severe ketosis was low. Severe ketosis after the onset of Addison's disease was often related to administration of cortisone in high dosage. The majority of the group had insulin hypoglycemia as one of the presenting symptoms of adrenocortic insufficiency. Twenty-nine of the group had hypoglycemia at some time; insulin dosage had to be reduced in all but 8 of the cases. Of the 17 known deceased patients, 5 died from adrenal insufficiency, 3 from infection, 3 from diabetic causes, and four from other causes. Complications reported included glomerulosclerosis, 2 cases of retinopathy, and 3 of retinal exudate, one of which appeared to be of "toxic origin."

In Group 3, which consisted of 5 patients, the two syndromes appeared to begin simultaneously. Four of the 5 patients are dead; the post mortem findings are distinguished by gross absence or severe malfunction of the adrenal cortex. No details of complications from either diabetes mellitus or Addison's disease are given.

In 44 cases, where both diseases are present before cortisone therapy, diabetes developed in only 20 per cent in the presence of already-established Addison's disease. Diabetes developed in 47 per cent of the cases recognized after cortisone therapy had been established. Although this increase in diabetes mellitus might suggest "unmasking" of latent diabetes by cortisone therapy, increasing life expectancy of patients with adrenocortical insufficiency might contribute. Hyperglycemia and acidosis have been reported to appear within weeks or even days after beginning cortisone therapy.

A final note tells of 3 newly reported cases of both Addison's disease and diabetes mellitus; 2 of these developed Addison's disease first.

Comment: From the point of view of ophthalmology, the most interesting part of this review article is the rarity of diabetic retinopathy in diabetic patients who have Addison's disease. Thus of 21 patients with Addison's disease who developed diabetes, none are described as having retinopathy; in 37 patients with diabetes who developed Addison's disease (20 of whom had adequate fundus examinations) only 2 patients with diabetic retinopathy were described. Such findings may be used as arguments for the possible role of the adrenal cortex in the pathogenesis of diabetic retinopathy.

BERNARD BECKER

REMISSION IN DIABETES

ARNOLD BLOOM

Whittington Hospital, London, England

Brit. M. J., 1959, *2:* 731–734

In some diabetics, and particularly in the young, there seems to be an absolute failure of insulin production. In diabetics of this type tolbutamide is ineffective, and permanent insulin is necessary to sustain life. On the other hand, in other diabetics, particularly in obese patients, the circulating insulin appears to be normal. In such cases the inherited defect may be no more than a functional disability of the pancreas to deal with abnormal stress situations. Mild diabetes will often remit to an apparently normal state when the stress situation has been removed, as is common experience in obese patients following a restricted diet or when an infection has been overcome.

However, some cases of diabetes are neither so severe as to need immediate insulin nor so mild as to respond to simple dietary restriction, and these patients today are commonly treated with tolbutamide or similar hypoglycemic agents. As a rule, weight and symptomatology are the factors deciding on choice of treatment.

The purpose of the present paper is to define the proportion of new diabetics controlled by these various means, and also to stress the dangers of unnecessary prolongation of insulin therapy. In 550 newly diagnosed diabetics referred to the Diabetic Unit of Whittington Hospital, largely during the period of 1952 to 1957, 184 (33.4 per cent) were adequately controlled by dietary restriction from the start, while a further 145 (26.3 per cent) were ultimately controlled by dietary restriction alone after temporary treatment with insulin or tolbutamide. The remaining 221 (40.2 per cent) needed permanent insulin or tolbutamide.

Interval supervision continues to be necessary after insulin or tolbutamide has been discontinued. Good control of the diabetic state requires normoglycemia, or near normoglycemia, and not merely freedom from symptoms. Hyperglycemia may carry with it ultimate dangers of degenerative changes in the arteries, kidneys, eyes, and nerves, and these changes have occurred in apparently mild and symptom-free diabetics where hyperglycemia was allowed to persist. Although it has been shown that remissions may last for many years, relapse may always occur, especially in the face of carelessness in diet or of infection.

Insulin is indicated in all young and severe diabetics, in diabetics where sepsis or gangrene exists, and, before the days of sulphonylurea therapy, in diabetics who continued to show glycosuria and hyperglycemia despite adherence to a suitable diet. The initial or hospital dose of insulin in new diabetics is often higher than that subsequently necessary to control the diabetic state. In some diabetics insulin requirements steadily diminish until eventually control is obtained on dietary restriction alone. If these patients are maintained without adequate supervision on the dosage of insulin originally necessary for control, chronic hypo-

glycemia may result. This can be particularly disastrous in elderly patients with a cerebral circulation impoverished by arteriosclerotic changes. In elderly patients relapse in the diabetic state can be less dangerous than the daily injection of insulin when the blood sugar is already below normal.

Comment: Patients with obesity and mild diabetes can develop diabetic retinopathy. On weight reduction the diabetes may no longer be apparent and one is faced with diabetic retinopathy without evidence of diabetes. Usually, such patients have a positive glucose tolerance test. The control of their diabetes without insulin may be used as an argument against the importance of control as a factor in the pathogenesis of diabetic retinopathy. It certainly tends to rule out insulin as a causative factor. The group of patients who are controlled on weight reduction and by diet alone offer excellent opportunities for studying diabetic retinopathy, its progression, and pathogenesis in the absence of severe metabolic disturbances and without the fluctuations induced by insulin or oral hypoglycemic agents. Interestingly enough in these patients the retinopathy appears to wax and wane much as it does in other diabetics.

BERNARD BECKER

SURGERY

INTERNISTS IN THE OPERATING ROOM

EDITORIAL

ROBERT D. DRIPPS

Surv. Anesthesiol., 1960, *4:* 127

The specialty of anesthesia has made great progress in providing better anesthesia for patients. The surgeons have challenged us to develop ways of permitting them to perform operations undreamed of 20 years ago. We have met that challenge. We now successfully deal with patients so ill that only a few years ago they would have been considered impossible surgical risks. We are discovering new and safer anesthetic agents, we are improving equipment, we are steadily expanding the usefulness of monitoring, we are training more specialists.

But few of us can develop new anesthetics, most of us are not sufficiently experienced to design better equipment, the wider use of monitoring devices requires considerable knowledge of electronics, and not many of us are in a position to train more anesthetists. Is there not some way in which the majority of us can contribute significantly to the progress of anesthesia, to the better care of the patient, some way which most of us have not yet explored?

We believe that the answer to this question is YES, that progress as important as any yet accomplished can be made in anesthesia if all of us in the field move

even further than we have in the direction of becoming internists or medical consultants to surgical patients. Such consultations might be relatively restricted, but they would certainly encompass aspects of cardiology, pulmonary disease and neurology. A broad background in medicine and therapeutics will be required.

As examples of the needs to be met, one can cite such important cardiologic aspects as the differential diagnosis of cardiac arrhythmias arising before, during and immediately after operation, the assessment of adequate digitalization, and the appraisal of preanesthetic tachycardia. An intimate knowledge of acid-base and fluid balance is essential, and the anesthetist must be familiar with the recognition and treatment of such abnormalities as hyponatremia, metabolic and respiratory acidosis, and changes in plasma potassium. Pulmonary function as related to normal and diseased man is being defined with increasing exactitude, but the bridge between laboratory and clinical practice is not yet well traveled. The application of measurements of function to clinical practice demand familiarity with the field by full time clinicians, and not just by investigators. The list can be expanded readily.

The specialty is being advanced along scientific lines by a few, but the majority must contribute by seeing to it that the art of anesthesia keeps abreast of the science. This, of course, includes continued improvement of technique and of clinical acumen as applied in the operating room. It means a proportionately greater share of patient care outside of the operating room. It also means increasing stature as physicians, with the added responsibilities that come with such stature. An anesthesiologist can offer much if he makes himself more of an internist than he now is.

Comment: All ophthalmic patients who undergo general anesthetic and many of those who might receive only local anesthesia could benefit from a preoperative and postoperative visit from a well trained anesthesiologist. These specialists are in a unique position to properly guide the choice of preoperative sedation, use of tranquilizers and analgesics, as well as those to be used after operation in each individual patient. There is no doubt that such cooperation reduces some of the complications which develop at the operating table as well as those which occur later.

IRVING H. LEOPOLD

CONTROLLED HYPOTENSION IN EYE SURGERY

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Ophthalmologica, 1959, *138:* 264–273

The ganglioplegic drug, Pendiomid, was administered intravenously in an operation for entropium and in 17 cases of dacryocystorhinostomy. The systemic blood pressure and intraocular pressure of the patients were measured daily for

several days before the operation. On the night before operation the patients were given 1 tablet of luminal and 2 of tablets Bellacorn. This dose was repeated the next morning about 1 hour before the operation. Half an hour later 1 ampule of Scophedal "mite" was introduced intramuscularly. The systemic and intraocular pressures were measured then and again after the patient had been placed on the operating table. The table was tilted at an angle of 30°. The patient's legs were allowed to slope down at an angle of 45° and the head placed somewhat lower than the thorax to assure a better blood supply to the brain. The ampule of Pendiomid was diluted in 2 ml. of saline giving 100 mg. of the drug in a 4-ml. solution. It was injected in doses of 25 or 50 mg. From 25 to 250 mg. (average 75 mg.) were needed to obtain and maintain a maximum fall of systemic blood pressure.

Seven of the patients were under and 5 were over 45 years of age. No correlation was found between the necessary dose and the age of the patient, his weight, blood pressure, etc. The Pentiomid reduced the blood pressure in the older group, all of whom had hypertension and in the 3 patients in the younger group who had hypertension. The decrease in blood pressure increased with the advancing age of the patient and initial blood pressure. It had practically no effect on the 4 younger patients who had a normal systemic pressure. The intraocular pressure decreased in 11 cases by 1 to 8 mm. Hg. No correlation, however, was found between the fall of intraocular pressure and the decrease of systemic arterial pressure.

In all cases in which the arterial pressure fell under the effect of Pendiomid the bleeding in the operation was practically negligible, thus enabling a reduction in the duration of the operation to 35 minutes.

An allergic reaction, manifested by an erythematous rash on shoulders, neck and thorax, occurred in one case. It disappeared within 10 minutes after intramuscular injection of Antistine.

Another ganglioplegic agent, Ecolid, was used in 6 cases of dacryocystorhinostomy. The procedure was the same as that when Pendiomid was used, except that the drug was introduced subcutaneously in a single 5-mg. dose immediately after the patient was placed on the operating table. The results were similar to those of Pendiomid. In a 35-year-old patient the systemic blood pressure showed practically no change, whereas in the others, aged over 43 years, it decreased. The intraocular pressure fell by 2 to 6 mm. Hg in all cases.

Comment: The authors discuss their own experiences with two ganglioplegic agents—Pendiomid intravenously and Ecolid subcutaneously—for production of purposeful hypotension during eye surgery. Eighteen cases in all were operated, 1 entropion plastic and 17 dacryocystorhinostomies. Apparently the ganglioplegic agents were used only in conjunction with local anesthesia, since no mention was made of any general or intravenous anesthetic. Their results seem to bear out this fact, for the younger age group and the normotensive individuals showed no hypotension which might have been obtained if general anesthesia were employed. The only blood pressure reductions occurred in the hypertensive and the older age groups. Their purpose in using the hypotensive agents was to produce a relatively bloodless operative field to facilitate the surgical procedure.

A review of the literature on controlled hypotensive anesthesia suggests that the technique should not be used unless it diminishes the risk of surgery due to excessive hemor-

rhage and facilitates the surgical result. Certainly the extent of hemorrhage encountered in a dacryocystorhinostomy should not present a risk to the patient's life from the standpoint of blood loss, and the technical advantage of a relatively bloodless field gained by the surgeon during the course of surgery must be carefully weighed against the possible complications of hypotensive anesthesia. The complications may be listed as follows:

1. Delayed postoperative recovery
2. Reactionary hemorrhage after hypotension
3. Difficulty with vision
4. Oliguria and anuria
5. Cerebral thrombosis
6. Coronary thrombosis
7. Cardiac arrest

All of these complications may occur as a result of anoxia, thrombosis, and postoperative hemorrhage either during or following the hypotensive state.

Definite contraindications to the use of hypotensive anesthesia are advanced coronary disease, angina pectoris, impaired renal function, and excessive hypertension. In this article the only patients who experienced hypotension with the technique described presumably with local anesthesia and Pendiomid or Ecolid were the hypertensive patients and the older age group, in which category one may expect more complications. However, if a ganglioplegic agent such as Arfonad were used with some type of general anesthesia, then controlled hypotension can be expected even with the young and normotensive patients. A technique that can be used is an intravenous drip of Arfonad solution (0.5 mg. per cc.) at the rate of 1 to 1.5 mg. per minute. With this rate the blood pressure returns to a normal level within 5 to 15 minutes after cessation of the infusion. With the technique described by Orłowski and Obniski (repeated doses of Pendiomid i.v. or a single subcutaneous dose of Ecolid) in those cases where hypotension was obtained return to normotensive state required several hours. This could be dangerous in the poorer risk patient.

If hypotensive anesthesia is to be used, it should be definitely controlled to the point where the pressure may be returned to normal levels within a very short period. The time element of hypotension should be short and only when the need for a bloodless field exists. The head position should be below the heart level to maintain adequate cerebral circulation. The administration requires careful observation even to the extent of using two people—one to watch the hypotensive phase and the other to maintain general anesthesia, if used. Effective lowering of the normotensive blood pressure should be at least to 80 mm. Hg systolic.

One can readily see the advantages of controlled hypotensive anesthesia in certain radical major surgical procedures where copious quantities of blood would be lost without it and enormous replacement transfusions would be required. Also in neurosurgery, especially cranial, where excessive hemorrhage would hamper the surgeon and impair the surgical result, hypotension for short periods could determine success or failure. However, in eye surgery such as dacryocystorhinostomy, where adequate hemostasis may be obtained with local anesthesia with vasoconstrictors, it is debatable whether the use of hypotension is warranted. Certainly the results of the ganglioplegic agents with local anesthesia as described by Orłowski and Obniski, where the hypotension seems unpredictable, do not warrant the risk of its use.

In conclusion, one can state that controlled hypotensive anesthesia in carefully selected cases, where the indications are clearly defined and is administered and controlled by trained personnel, has a limited application in ophthalmic surgery.

SAMUEL BLANK

THERAPEUTICS

THE EFFECTS OF ANTICHOLINESTERASE AGENTS ON THE BLOOD CHOLINESTERASE LEVELS OF NORMAL AND GLAUCOMA SUBJECTS

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NARENDA KRISHNA, AND ROBERT A. LEHMAN

New York, New York

Tr. Am. Ophth. Soc. 1959, *57:* 63–86

Anticholinesterases are used locally in treating glaucoma. In primary glaucoma their effects on the iris, ciliary body, and blood vessels of the eye lower intraocular pressure. In closed-angle glaucoma their miotic action frees the angle from obstruction by the iris. In open-angle glaucoma they improve aqueous outflow either by their effect on the ciliary body or on the blood vessels.

Cholinesterase inhibition preserves acetylcholine from hydrolysis, allowing it to perform its full muscarinic action on the iris, ciliary body, and blood vessels. These tissues, like the erythrocytes, contain Group I cholinesterases or acetylcholinesterases, which are concerned in neurohumoral functions of acetylcholine. The plasma contains Group II cholinesterases, which are not concerned in neurohumoral transmission.

The cholinesterase content of the iris and ciliary are not known in cases of glaucoma, but the levels in whole blood of these patients is well within normal limits. Since anticholinesterases are used continuously over a long period in treating glaucoma, some of these drugs are probably absorbed. The present study is designed to determine the effects of anticholinesterases on the red blood cell and plasma cholinesterase levels of normal persons and patients with glaucoma. Cholinesterase determinations were carried out by the method of continuous titration at constant pH. The drugs used were physostigmine, salicylate, prostigmine methylbromide, DFP, phospholine-iodide, and Humorsol.

Nineteen patients with glaucoma showed consistently lower cholinesterase levels in the red blood cells than did 20 normal persons. Cholinesterase activity varies widely among individuals, but is rather consistent in any one individual.

A control blood sample was then taken from each normal person and also samples were taken 3 and 5 hours after instillation of maximal therapeutic doses into the eye. Because diurnal fluctuations were unknown, only values less than the normal mean less two standard deviations were considered significant. Using this standard, the cholinesterase levels of the red blood cells were de-

pressed in one person after 0.5 per cent Humorsol, the depression lasting 1 to 5 hours after instillation. No effects were noted after giving the other test drugs.

Patients with long-standing glaucoma were then given the smallest doses of anticholinesterase which would control intraocular pressure, and blood samples were collected 1, 2, and 3 weeks after the initiation of therapy. Of 11 patients suitable for study, only 1, who was on Humorsol, showed significant depression of the erythrocyte cholinesterase level at the 2- and 3-week interval. Other patients showed no change.

Samples taken from patients who had been on anticholinesterase therapy at least 2 months were also tested. Of 9, 2 receiving physostigmine, 11 of 12 on phospholine, and 5 of 8 on Humorsol, had red-cell cholinesterase levels significantly depressed. Of 9 on phospholine 2 had depressed plasma cholinesterase, and 9 on DPF were unaffected.

Such studies must be made after eliminating physical conditions which might affect cholinesterase levels, and also only when no drugs are being given which might affect the results. The present study shows that instillation of anticholinesterases into the eye may lead to enough absorption to affect red blood cell and plasma cholinesterase levels. None of the patients in this study had undesirable side effects, but such effects should be expected in some cases.

Comment: Of the various studies of metabolic and biochemical anomalies in glaucoma patients as compared to normals, this study may be the most significant if the findings are confirmed in additional patients. The further lowering of the erythrocyte cholinesterase levels by the cholinesterase inhibitors may cause clinical changes which we do not as yet recognize.

SAUL SUGAR

(*Editor's note:* The following eight papers are devoted to studies on and uses of fibrinolysin. The first seven were part of a special issue of ANGIOLOGY and the eighth appeared in the CANADIAN MEDICAL ASSOCIATION JOURNAL. Editorial comments are found on page 591.)

EARLY EXPERIENCE WITH FIBRINOLYSIN

EUGENE E. CLIFFTON

New York, New York

Angiology, 1959, *10:* Part 2, 244–252

The ability of fibrinolytic activity to dissolve thrombi is no longer questioned, but understanding has been clouded by semantic problems and by the use of different experimental materials which were not fully comparable.

Plasminogen is regularly defined as the inactive precursor of fibrinolytic (proteolytic) activity produced by various means. Plasmin is defined as the fibrinolytic enzyme produced by activation of plasmogen. The two theories of activation—usually by streptokinase—can be resolved best by considering plasminogen as a homogenous protein capable of producing activator or enzyme according to the particular chemical reactivity produced, and by considering plasmin as capable of acting both as activator and as enzyme. Fibrinolysis and thrombolysin are synonyms for plasmin. A kinase is any material which reacts upon plasminogen.

We do not know whether plasmin is necessary for lysis, or whether a kinase alone is adequate. At present we recommend a ratio of 500 units per mg. of plasminogen, which gives optimal activation *in vitro* and has also given good clinical results. We do not favor the use of kinase alone. A common unit for reporting activity in patients is needed and should be agreed upon.

We have not seen significant effects in patients unless doses close to 4 mg. per kg. were given and lytic activity observed in the blood. We think that divided "priming" doses for 24 hours before infusion increases the effect of the infusion, but that a longer delay has the opposite effect. This may be related to changes in fibrinogen and inhibitor levels. Our studies *in vitro* and animal studies have shown that increased fibrinogen leads to slower lysis.

Thirty-eight of our series of 76 patients with various types of thrombosis have been treated for venous thrombosis of 16 hours to 9 months duration. Thirty-four had subjective and 31 definite objective signs of improvement; 21 were completely relieved of symptoms and 16 became objectively normal after 1 to 7 days of treatment.

Ten cases have been treated for arterial thromboses, with variable results. Combinations of operation with general or local, especially local, therapy, have been successful in treating thrombi, but other complications have negated results in some instances. Four of five with pulmonary embolus were completely relieved. Treatment of retinal thrombi was not definitive.

Among 200 cases treated locally and in 100 treated by infusion we have seen no sensitivity reactions, nor have we seen serious decrease in the clotting mechanism. We have, however, hesitated to combine anticoagulant therapy with plasmin therapy. Some evidence suggests that plasmin therapy may spread infection, but we have found that the pyogenic response, especially in older persons or in those with serious disease, is the chief danger. Such reactions have been less frequent in treating arterial than venous thrombi.

(*See editorial comments, p. 591.*)

INTRAVENOUS ADMINISTRATION OF FIBRINOLYSIN: ITS SYSTEMIC TOXICITY AND EFFECT UPON COMPONENTS OF THE COAGULATING MECHANISM

KENNETH M. MOSER

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Angiology, 1959, *10:* Part 2, 253–258

The toxic-therapeutic ratio of fibrinogen has been studied in 72 infusions of 63 patients, with various dosage levels. Blood samples were taken before and 24 hours after infusion, and in most instances at 3 or 6 hours, or both, after infusion. Laboratory studies, electrocardiograms, and skin tests were also carried out.

Systemic toxicity was manifested almost entirely by elevation of temperature, which occurred in 44.4 per cent of infusions. The incidence and degree of elevation did not seem related to dosage. Study to date suggests that the fever is more probably due to activated fibrinolysin than to the plasminogen, which is not pyogenic in animals, or to the activity of fibrinogen *in vivo*, which we have not found coordinated with the fever. Fever does seem to correlate with the presence of large zones of thrombus. The pyogenic effects can be mitigated or prevented by salicylates or other antipyretics. Most of the patients who reacted with fever also had nausea or chills or both, and two had urticaria. No significant toxic effects on the renal system were noted, but two had cardiac symptoms at the height of the fever.

Our preliminary studies show that at the doses used, fibrinolysin causes only minimal changes in coagulation factors or parameters. Less than half the patients had more than a 5 per cent decline in coagulation time, prothrombin time, or recalcification time. Proaccelerin and prothrombin were unchanged. Fibrinogen usually fell more than 5 per cent below base levels at 3 and 6 hours after infusion, and changes in degree were also greatest in fibrinogen. None of the changes observed were, however, likely to impair coagulation. Moreover, 29 patients who received anticoagulants and fibrinolysin at the same time showed no signs of hemorrhage.

We assessed lysis by adding to the patient's blood a standard amount of fibrinogen and thrombin. A firm clot formed, and was observed for evidence of lysis. If lysis time decreased 10 per cent and required less than 25 minutes, it was considered evidence of increased lytic activity. According to this test, fibrinolysin enhanced the fibrinolytic property of the blood in 84.6 per cent of patients. The incidence and intensity of lysis were functions of the dosage. However, because of numerous complex variations, test-tube observations cannot yet be used as exact criteria of clinical dosage, which still remains empirical.

(*See editorial comments, p. 591.*)

THE USE OF FIBRINOLYSIN IN THE PREVENTION OF THROMBUS FORMATION IN SMALL ARTERY ANASTOMOSES

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Angiology, 1959, *10:* Part 2, 259–262

Following operations on blood vessels of 4 mm. or less in diameter, thrombi may form at the suture line, causing occlusion. Some thrombus formation is essential to control bleeding, but if it could be stopped at this point many fewer failures would occur.

End-to-end anastomoses were performed on 42 femoral arteries of small dogs, the diameters of the vessels being 2.5 to 4 mm. Anastomosis was triangulated with three guide sutures, and simple over-and-over sutures of 0-6 silk were placed between them, with atraumatic needles. Bleeding was controlled by gentle pressure at the suture line. Fibrinolysin was given by slow intravenous drip, using 10,000 to 20,000 units in 10 or 250 cc. of normal saline before, during, or after operation, or at a combination of these times.

A total of 33 per cent of these arteries remained patent compared to 42 per cent of 12 controls. Rather wide variations in concentration or dosage or time did not seem important. Possibly the unpurified human product was not effective in dogs, but more probably the doses were too small. No adverse effects were noted. Further study with larger and more frequent doses would seem warranted.

(*See editorial comment, p. 591.*)

THROMBOLYSIS WITH FIBRINOLYSIN IN CEREBRAL ARTERIAL OCCLUSION: THE ROLE OF ANGIOGRAPHY

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Angiology, 1959, *10:* Part 2, 268–282

A cerebral arterial occlusion can be clearly diagnosed and located and the effect of a thrombolytic agent evaluated with reasonable accuracy by means of carotid arteriograms. The present study is designed to determine by angiography whether cerebral arteries can be cleared of thrombi by fibrinolysin, under what circumstances, and how rapidly.

Nine case histories are reported, illustrated by arteriograms and photographs of post mortem specimens. In several cases the nature of the occluding lesion remained uncertain, even when pathologic and roentgenographic evidence was

excellent. Angiograms do, however, help to distinguish thrombi from transient or permanent hemiplegia, increasing the chances of using fibrinolysin only in suitable cases. While the posterior cerebral artery rarely fills and the anterior occasionally fails to fill, failure of the middle cerebral artery to fill always indicates occlusion, pressure, or spasm, the pictures of which are usually distinctive. It also seems likely from our experience that angiograms showing that the middle cerebral artery has cleared can be considered reliable. In two cases, the angiograms suggested complications from anticoagulants.

The efficacy of fibrinolysis in clearing cerebral thrombi cannot be determined conclusively from this study. In 4 cases, occluded arteries became patent after treatment, and in 2 the lumen was partly restored; but in 3 no change could be observed. The immediate results of fibrinolysin therapy may depend on the patient's ability to produce inhibitors and activators of the enzyme.

(*See editorial comments, p. 591.*)

THE TREATMENT OF PULMONARY EMBOLISM WITH FIBRINOLYSIN

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Angiology, 1959, *10:* Part 2, 292–298

The high incidence, morbidity, and mortality from pulmonary embolism in hospitals make this condition a very serious problem. No altogether practical method of prevention is available, and anticoagulant treatment, though of proved value, has its drawbacks. Fibrinolytic enzymes offer a possible answer.

Thirty-three patients have been treated with infusions of fibrinolysin for various thrombic or embolic diseases, and the case histories of the six treated for pulmonary embolism are reported. The efficacy of the treatment is judged by the speed of resolution of the thrombus as demonstrated by changes in roentgenograms and electrocardiograms, improvement of symptoms, and the incidence of recurrences.

Febrile reactions beginning within 2 hours of infusion occurred in 84 per cent of the entire series of 33 patients. Two of those with pulmonary embolism who were not receiving anticoagulants later had infarcts. No signs of hemorrhage, coagulation impairment, or urea retention or albuminuria were observed, and electrocardiograms were not affected.

Roentgen shadows of pulmonary embolism disappeared rapidly in 4 of 6 cases. Associated acute phlebitis was also resolved, and in two instances chronic phlebitis was improved. This improvement in roentgenograms and in clinical symptoms was much more rapid than in controls, and there were no recurrences in those who also received anticoagulants. Acute symptoms were rather con-

stantly relieved, but symptoms of long-standing disease were only transiently alleviated.

Fibrinolysin may prove a useful supplement to anticoagulant therapy, but more study is needed.

(*See editorial comments, p. 591.*)

CLINICAL OBSERVATIONS IN THE TREATMENT OF PHLEBOTHROMBOSIS WITH FIBRINOLYSIN

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Angiology, 1959, *10:* Part 2, 308–310

Anticoagulants may prevent extension or recurrence of thrombi, but do not lyse formed thrombi. Various proteolytic enzymes have proved disappointing or dangerous, but fibrinolysin has been demonstrated to show preferential lytic action on fibrin. It has now been purified and is known not to disturb the clotting mechanism.

Doses of 25,000 to 50,000 units, recently with the latter as the initial dose, have been given in 250 cc. of isotonic saline by intravenous infusion to 78 patients with thrombophlebitis, repeating the dose if necessary to a total of 100,000 units. At first we used anticoagulants before fibrinolysin, but now we reverse the order. Thirty-nine received the two simultaneously with no undesirable effects.

Of 83, 60 had excellent results, and 19 good response, consisting of alleviation of pain, edema, and inflammation, and restoration of movement. Fever was controlled by aspirin or Demerol. There were no cases of postphlebitic syndrome and no recurrences during a short period of observation. A pulmonary embolism appeared in one patient during therapy, but resolved on continued treatment.

(*See editorial comments, p. 591.*)

CLINICAL OBSERVATIONS IN THROMBOEMBOLIC DISEASE TREATED WITH FIBRINOLYSIN

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Angiology, 1959, *10:* Part 2, 319–331

The authors present a preliminary report of fibrinolysin therapy of 128 patients with various types of thrombi.

Of 41 treated for deep venous thrombosis, those treated within 5 days of onset were always improved, and fully relieved if the initial dose was 75,000 to 100,000 units. Second doses were given after 18 to 24 hours if needed. Patients were kept in bed 1 day after relief of symptoms and anticoagulants given for 2 or 3 days, beginning with ambulation. This method seems to decrease the incidence of pulmonary embolism, postphlebitic syndrome, and recurrence, provided the anticoagulants were used.

Judging from the incidence of recurrence, restoration of normal hemodynamics, and clinical improvement, lytic-anticoagulant therapy was also effective in 7 of 13 cases of pulmonary embolism; failures in three instances were in old cases or catastrophic disease. Thirty-eight were treated for arterial thrombosis. Because of the time factor, clot dissolution could not be judged by clinical symptoms in the 22 with cerebral occlusion. Acute arterial occlusion in the extremities was improved if it was treated within 24 to 96 hours of onset. We have used higher doses in arterial thrombosis than in venous cases since the time factor seemed to warrant more potent and sustained treatment.

(*See editorial comments, p. 591.*)

THE SUCCESSFUL TREATMENT OF A CASE OF CENTRAL RETINAL VEIN THROMBOSIS WITH INTRAVENOUS FIBRINOLYSIN

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Canad. M. A. J., 1959, *81:* 382–384

Central retinal vein occlusion in older patients with arteriosclerosis usually leads to loss of vision to 20/200 or less. Anticoagulant therapy has proved rather ineffectual. Some reports have suggested that lysis by means of fibrinolysin improves the condition and that it does not recur after this type of therapy.

A 63-year-old man was admitted with dim vision in the right eye of two days' duration, a history of intermittent crampy pain in both legs for 10 years and some shortness of breath for 5 years. He had been deaf for 3 years and had not felt well for the last year. Physical examination showed good general health. The right eye saw hand movements only, the optic disk was swollen and the veins dilated, with hemorrhages dotting the entire retina and deformed arteriovenous crossings. The diagnosis was central vein thrombosis.

The patient was given 100,000 units of fibrinolysin and 50 mg. of diphenhydramine by intravenous infusion in 250 cc. of saline, and the treatment was repeated the next 2 days. On the 3rd day, acenocoumarin was started. The patient had a febrile attack, and erythema started at the point of injection and spread

over the whole body, but responded to chlorphenhydramine. Vision gradually improved and symptoms regressed on maintenance doses of anticoagulants. Two months after admission vision in the affected eye was 20/25.

Comment: Plasmin has been under study for clinical purposes for almost 5 years but has received intensive study in many areas only within the past 2 or 3 years. Its use in pulmonary embolism, thromboembolic disease and in arterial occlusion has been pursued in many institutions and, as yet, results are not conclusive but they are certainly very suggestive of the importance of this compound in vascular medicine, particularly to those interested in research in this area. Our experience with this agent in central vein occlusions and central artery occlusions has not been impressive to date. Even in early cases, ones which we believe were treated within 72 hours of onset, there have been failures. All ophthalmologists know that spontaneous recoveries can occur. It is difficult to evaluate clinically the benefit of this type of therapy except in large series with alternate case techniques and other control features. The agent has definitely been toxic to a number of people, producing fever reactions particularly. As the drug companies have purified this and reduced the amount of contained streptokinase, a certain amount of which is necessary for activation of the precursor in the blood, the reactions have reduced. Dr. David Warner at the Wills Eye Hospital has been using this medication to aid in the clearing of intraocular hemorrhages and, although he can demonstrate some benefits in a standard experimental lesion, it is extremely difficult to be certain of its beneficial influence on clinical intraocular hemorrhagic lesions. There are various methods by which one can be certain of the level of fibrinolytic activity in the blood and it would seem advisable, at this stage of our knowledge, to follow all patients who are receiving the drug with tests which will determine the presence of adequate quantities of lytic factor in the circulating system. We have had anticoagulants with us for years and still the results with this agent in central vein occlusions and central artery occlusions have not been clear cut. Theoretically, the combination of a fibrinolytic agent such as fibrinolysin with anticoagulant therapy would appear to be ideal for vascular closures in the eye but we have to be able to separate those occlusions which are predominantly due to thickening of the wall and narrowing of the lumen due to organic changes in the wall from those which are essentially due to closure of the lumen by clot formation. The ballot has not been counted on this agent as yet.

IRVING H. LEOPOLD

TREATMENT OF HERPES ZOSTER OPHTHALMICUS WITH CORTICOTROPIN AND CORTICOSTEROIDS

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A. M. A. Arch. Ophth., 1959, *62:* 579–587

In the present paper further observations on the treatment of herpes zoster ophthalmicus with corticotropin and corticosteroids are offered. It continues the report by Scheie and Alper (A. M. A. Arch. Ophth., *53:* 38, 1955). The treatment

and course of 25 more patients with herpes zoster ophthalmicus who have been treated with hormones given systemically are summarized.

It is difficult to assess therapy in a disease like herpes zoster ophthalmicus, which may show spontaneous remission and whose severity is hard to quantitate. In the authors' experience systemic treatment with corticotropin and corticosteroids has been the only successful alternate to convalescent blood therapy. In convalescent blood therapy the difficulty of procuring donors and the hazard of reactions with frequent transfusions are encountered. On the Dermatology Service of the Hospital of the University of Pennsylvania corticotropin and corticosteroids are used in severe cases of herpes zoster, especially for those patients who have severe pain or deep skin lesions. Most such patients receive oral triamcinolone, but those with gangrenous or very widespread painful lesions are given intravenous corticotropin.

In a total of 36 patients with herpes zoster ophthalmicus treatment with systemic corticotropin and corticosteroids was carried out. Significant visual loss has occurred in only two eyes. The commonest complications of herpes zoster ophthalmicus are iridocyclitis and corneal opacity. Recurrences of iridocyclitis and keratitis after the initial attack subsides can be suppressed readily with corticosteroids. Such recurrences seem to improve as rapidly with hormone treatment as does the initial attack.

It is to be emphasized that those patients who do not improve initially on systemic therapy with corticotropin and corticosteroids do respond when the dose of corticotropin is increased to 60 to 80 units daily. None of the patients in this series have shown any exacerbation of the disease which might be attributable to hormone treatment.

The courses of seven of the patients indicate that the hormones have little if any effect on the virus which causes herpes zoster, but that they act in a protective manner during the acute period of involvement. One of the patients developed herpes zoster ophthalmicus accompanied by iridocyclitis and corneal infiltrates, while receiving oral corticosteroid therapy for leukemia. His ocular inflammation quieted after the dose of steroid was increased.

Results of treatment seem to indicate that systemic corticotropin and corticosteroids exert a very favorable effect on herpes zoster ophthalmicus.

Comment: There are in the literature a number of references which consider this very subject.

A. Report of Cases of Herpes Zoster Improved or Course Unaltered While Patient Getting Steroid or ACTH Therapy.

1. Treatment of Ophthalmic Zoster with Prednisone. A. B. Carter, and J. E. Royds, Brit. M. J., *5047:* 746, Sept. 28, 1957.

Fifteen cases of herpes zoster ophthalmicus treated with prednisolone resulted in less edema. The rash dried quicker and the scarring was reduced. No fresh vesicles developed on therapy. Pain was less than in the control group. There was no effect on incidence of ophthalmic complications, *e.g.*, conjunctivitis, keratitis, iridocyclitis; 1 patient went on to panophthalmitis and 1 proceeded to a severe postherpetic neuralgia.

2. Treatment of Herpes Zoster with ACTH. D. H. Appelman, New England J. Med., *253:* 693, 1955.

ACTH gave dramatic relief of pain in 4 of 5 patients with herpes zoster. One of these had herpes zoster ophthalmicus but the course of the pathologic process on the skin was unaltered. One patient with postherpetic neuralgia failed to respond.

3. Herpes Zoster. Treatment of Postherpetic Neuralgia with Cortisone, Corticotropin and Placebo. G. C. SAUER, A.M.A. Arch. Dermat. & Syph., *71:* 488, 1955.

ACTH and cortisone effective in relief of pain in 70 per cent of 15 cases while a placebo was effective in 36 per cent of the cases.

4. Herpes Zoster of Face and Neck with Paralysis, Earache, Dizziness and Nausea (Ramsey Hunt Syndrome). Connecticut M. J., *19:* 103, 1955.

One case benefitted with ACTH.

5. Treatment of Herpes Zoster Ophthalmicus with Cortisone and Corticotropin. H. G. SCHEIE AND M. C. ALPER, A.M.A. Arch. Ophth., *53:* 38, 1955.

In 11 patients with herpes zoster ophthalmicus there was relief of pain, suppression of ocular inflammation but not regarded as curative.

6. Treatment of Herpes Zoster with Cortisone. J. P. DOENGES, Illinois M. J., *106:* 131, 1954.

Fifteen cases treated with cortisone, cortisone and chloramphenicol, and chloramphenicol alone. Author found no proved superiority of any of these although he thinks cortisone may be of some value in herpes zoster ophthalmicus.

7. Treatment of Herpes Zoster with Cortisone. N. L. GELFAND, J.A.M.A., *154:* 911, 1954.

Favorable response in 4 of 5 patients—2 of the 5 had herpes zoster ophthalmicus and 1 of these 2 did not show dramatic improvement.

8. Mandibular Herpes Zoster with Report on the Use of Cortisone in a Case of Geniculate Ganglion Symptoms. I. M. SHEVICK, California Med., *79:* 444, 1953.

No apparent therapeutic effect in the 1 case described.

9. Value of ACTH in Herpes Zoster Ophthalmicus. J. E. POULIN, Maine M.A., *43:* 301, 1952.

Three cases of Herpes Zoster Ophthalmicus failed to respond to cortisone topically or systemically but did respond dramatically to ACTH i.m. within 48 hours.

10. Herpes Zoster Treated with ACTH. W. R. NICHEL, A.M.A. Arch. Dermat. & Syph., *64:* 372, 1951.

Reported good result in herpes zoster but of no value in postherpetic neuralgia (*Current Therapy*, Saunders, 1957, p. 559).

B. Reports of the Spontaneous Appearance of Herpes Zoster or of the Occurrence of Prolonged, Complicated Courses of Herpes Zoster While on Steroid Therapy.

1. Herpes Zoster Appearing during Cortisone Therapy: Case Report. H. C. FISHMAN, Ann. West. Med. & Surg., *5:* 487, 1951.

Report of 1 patient with rheumatoid arthritis who while receiving a daily maintenance dose of 65 mg. of cortisone i.m. developed herpes zoster lesions on the right shoulder during the 8th month of therapy. The author concluded on the basis of this experience that cortisone neither protected against virus diseases like herpes zoster nor alleviated the pain associated with it but did hasten the involution of the skin lesions.

2. J. C. GILBERT, in Queries and Minor Notes. J.A.M.A., *152:* 1394, 1953.

Commented that he had 2 patients who developed herpes zoster while taking cortisone acetate and 1 patient that developed herpes zoster while taking corticotropin.

3. Herpes Zoster during Cortisone Therapy in Three Patients with Rheumatoid Arthritis. H. G. KUPPERMAN, J. S. DAVIS, JR., AND H. BARTFELD, New York J. Med., *52:* 1915, 1952.

TABLE 1

Summary of Findings and Therapy on 25 Patients with Herpes Zoster Ophthalmicus

No.	Age, Yr.	Date of Onset	Eye	Predominant Eye Manifestation	Systemic Hormonal Therapy				Course of Ocular Lesions	Sequelae
					Substance	Daily Dose	Route	Duration, days		
1	56	4/30/54	Right	Iridocyclitis	Acthar	40 u.	I. M.	9	Pain subsided in 2 days; iridocyclitis cleared in 12 days; topical steroid therapy continued to 1 mo.	None
2	34	6/ 5/54	Left	Iridocyclitis, with corneal edema	ACTH	20 u.	I. V.	3	Subsided in 4 days	None
					Acthar	40 u.	I. M.	1		
3	37	1/24/55	Right	Uveitis, severe; many K. P.; marked edema and thickening	ACTH	20 u.	I.V.	3	Initial attack subsided; recurrence in 48 days with tension of 46; suppressed with systemic hormones; two further recurrences suppressed with topical therapy	Permanent corneal edema. Recurrent iridocyclitis, visual acuity 6/24
					Acthar	40 u.	I. M.	3		
					Cortisone	50 mg.	Oral	25		
4	64	2/15/55	Left	Iridocyclitis; punctate staining of cornea	ACTH	20 u.	I. V.	3	Subsided in 18 days	None
					Acthar	40 u.	I. M.	9		
					Cortisone	50 mg.	Oral	28		
5	55	3/ 3/55	Left	Iridocyclitis; corneal edema	ACTH	40 u.	I. V.	2	Little initial response; subsided after 5th day on increased dose	None
					Acthar	20 u.	I. M.	2		
					Acthar	40 u.	I. M.	7		
					Cortisone	50 mg.	Oral	26		
6	66	5/10/55	Left	Iridocyclitis, marked corneal edema with folds in Descemet's membrane	ACTH	40 u.	I. V.	2	Subsided in 2½ wk.	Iridoplegia
					Acthar	40 u.	I. M.	5		
					Cortisone	50 mg.	Oral	30		
7	57	8/18/55	Left	Iridocyclitis, corneal edema	ACTH	40 u.	I. V.	3	Subsided in 3 wk.	None
					Athar	80 u.	I. M.	7		
					Prednisone	20 mg.	Oral	13		
8	7	10/11/55	Left	Iridocyclitis, corneal edema	Acthar	40 u.	I. M.	13	Subsided in 2 wk.	None
					Acthar	20 u.	I. M.	1		
					Acthar	20 u.	I. M.	1		
9	62	3/ 5/56	Right	Iridocyclitis, corneal edema	Acthar	40 u.	I. M.	7	Subsided in 14 days	None
					Acthar	Tapered	I. M.	7		
					Prednisone	10 mg.	Oral	21		
10	8	5/ 8/56	Left	Uveitis	Acthar	40 u.	I. M.	10	Subsided in 1 mo., one mild recurrence of iridocyclitis at 6 mo., suppressed with topical treatment	None
					Acthar	20 u.	I. M.	3		
					Acthar	10 u.	I. M.	2		
					Acthar	5 u.	I. M.	1		
					Cortisone	100 mg.	Oral	15		
11	55	7/ 1/56	Left	Iridocyclitis, secondary glaucoma	ACTH	40 u.	I. V.	5	Tension normal in 1 day; gradual clearing in 13 days; one mild recurrence suppressed with oral cortisone	Corneal scar, visual acuity 6/12
					Acthar	40 u.	I. M.	6		
					Prednisolone	20 mg.	Oral	7		

12	72	10/30/56	Left	Iridocyclitis	ACTH	20 u.	I. V.	3	Subsided gradually	Corneal scar, visual acuity 6/9
/					Prednisone	20 mg.	Oral	12		
13	76	11/30/56	Right	Iridocyclitis, corneal edema	Acthar	80 u.	I. M.	3	Subsided in 7 days	None
					Acthar	20 u.	I. M.	4		
14	69	12/ 1/56	Left	Iridocyclitis, secondary glaucoma	Acthar	40 u.	I. M.	5	Tension normal in 2 days; one recurrence with episcleritis suppressed with oral prednisone	None
					Prednisone	20 mg.	Oral	15		
15	60	2/26/57	Left	Uveitis, severe; many K. P.; corneal edema; secondary glaucoma (T-60 mm. Schiøts)	ACTH	40 u.	I. V.	3	Controlled promptly by hormonal therapy; tension normal with addition of acetazolamide; repeated recurrences over 2 yr.; controlled by oral and topical corticosteroid therapy	Repeated recurrences iridoplegia
					Acthar	40 u.	I. M.	5		
					Acthar	60 u.	I. M.	2		
					Prednisone	20 mg.	Oral	16		
16	57	4/ 1/57	Right	Iridocyclitis	ACTH	40 u.	I. V.	3	Subsided in 12 days	None
					Acthar	80 u.	I. M.	4		
					Prednisolone	20 mg.	Oral	3		
17	49	4/11/57	Right	Iridocyclitis, herpetic corneal infiltrates (developed herpes while taking prednisone 15 mg. daily, mycosis fungoides)	Prednisone	20 mg.	Oral	43	Prednisone increased to 20 mg.; subsided promptly; died of leukemia 43 days after onset of herpes	Eye quiet at death
18	65	6/17/57	Right	Iridocyclitis, corneal edema	ACTH	20 u.	I. V.	3	Subsided in 5 wk.	Optic atrophy noted at 6 wk.
					Acthar	40 u.	I. M.	4		
					Prednisolone	10 mg.	Oral	39		
19	56	7/ 9/57	Right	Iridocyclitis	ACTH	20 u.	I. V.	4	Subsided in 3 wk.	None
					Acthar	40 u.	I. M.	2		
					Prednisolone	10 mg.	Oral	8		
20	66	2/13/58	Right	Uveitis; many K. P.; corneal edema; secondary glaucoma (tension-36 mm. Hg)	ACTH	40 u.	I. V.	1	Tension normal in 1 day, subsided in 18 days	None
					ACTH	20 u.	I. V.	4		
					Acthar	40 u.	I. M.	1		
21	27	3/23/58	Left	Iridocyclitis	ACTH	40 u.	I. V.	4	Subsided in 5 days	None
					Acthar	40 u.	I. M.	2		
22	68	7/ 2/58	Left	Uveitis, herpetic corneal infiltrates	Acthar	40 u.	I. M.	1	Intense pain subsided on increased dose of ACTH intravenously; on change to prednisolone pain recurred; change to methyl prednisolone with dramatic relief; 1st attack subsided; recurrent iridocyclitis; controlled on each occasion with methyl prednisolone	Recurrent iridocyclitis
					ACTH	60 u.	I. V.	1		
					ACTH	40 u.	I. V.	2		
					ACTH	25 u.	I. V.	7		
					Prednisolone	16 mg.	Oral	4		
					Methyl prednisolone	16 mg.	Oral	21		
23	68	8/10/58	Right	Iridocyclitis, herpetic corneal infiltrates	Acthar	40 u.	I. M.	4	Subsided in 6 days	None
					Prednisolone	20 mg.	Oral	8		
	51	11/ 8/58	Left	Iridocyclitis, secondary glaucoma	ACTH	40 u.	I. V.	4	Subsided in 8 days, recurrences with secondary glaucoma suppressed with methyl prednisolone	Recurrent iridocyclitis
					Acthar	40 u.	I. M.	4		
					Methyl prednisolone	16 mg.	Oral	15		
25	67	12/ 1/58	Left	Iridocyclitis, severe; corneal edema	ACTH	40 u.	I. V.	6	Little change on initial dose; improved on increased dose, then subsided satisfactorily	None
					ACTH	60 u.	I. V.	2		
					ACTH	40 u.	I. V.	3		
					Methyl prednisolone	16 mg.	Oral	60		

The authors do not give the total number of patients observed—merely describe 3 cases. (We therefore do not know the incidence.) These authors believe this is a coincidental occurrence because more cases of this complication would have been reported if it weren't. They observed that cortisone had no effect on the herpes zoster course (*i.e.*, worse or better).

4. Herpes Zoster of Prolonged Evolution Complicated by Cutaneous Gangrene during Cortisone Therapy. A. G. DE MACEDO AND M. B. DA S. MOREIRA, Rev. brasil. med., *11:* 97, 1954.

Case presentation: A 26-year-old male with Boeck's sarcoid after 39 days of cortisone therapy developed herpes zoster with sacral, cervical and thoracic lesions. During the next 22 days the pain persisted and the lesions progressed to the point of necrosis and gangrene in the skin lesions of the legs. Steroids were stopped for 7 days. The lesions then began to subside. Steroid therapy was restarted; the skin lesions continued to improve but slowly. The duration of the herpes zoster disease was 42 days.

5. Severe Necrotic Herpes Zoster with General Spread in One Case during Treatment of Blood Disease with Corticotherapy. J. DUVERNE, B. MULLER, R. MOUNIER, AND BLANCHET. Bull. Soc. franç. dermat. et syph., *64:* 433, 1957.

Report of 2 cases. One case is that of an 11-year-old girl with lymphoblastic leukemia who was treated with blood transfusion, antibiotics, hydrocortisone, deltacortisone and 6 mercaptopurine during a 2-month period. The patient was discharged. Has improved on steroid therapy. One month later the girl was readmitted with thoracic herpes zoster. The lesions were necrotic and initially very painful. Her general and blood condition were good. The course of the herpes zoster was prolonged with large necrotic skin areas but with minimal pain. Cicatrization began after 1 month.

Case 2 was that of a 71-year-old male who was given chloramphenicol and pyridoxine for lymphoblastic sarcoma. Several weeks later cortisone therapy was started. The patient was discharged about 3 weeks later in good condition. Nine days later he was readmitted with herpes zoster ophthalmicus—necrotic skin lesions, lid edema, conjunctivitis but no keratitis. Eight days later the lesions became disseminated over the entire body. The lesions improved after 2 weeks.

6. Serious Untoward Reactions to Therapy with Cortisone and Adreno-Corticotropin in Pediatric Practice. R. A. GOOD, R. L. VERNIER, AND R. T. SMITH, Pediatrics, *19:* 95, 1957.

In a large group of children being treated with steroids and ACTH for various serious diseases severe herpes zoster infections developed spontaneously in 2 patients.

7. Cortisone and Herpes Zoster. Editorial. New England J. Med., *261:* 517–518, 1959.

In 1951 Duke-Elder[1] described improvement in 4 cases of herpes zoster iridocyclitis treated with cortisone. Other cases of herpes zoster, reported at about the same time, showed variable responses to treatment with ACTH and cortisone.[2] Carter and Royds[3] discussed the treatment in 1956 of 15 consecutive cases of ophthalmic herpes zoster with prednisone and antibiotics and compared the results with those observed in a similar group treated without prednisone in 1951. They considered that prednisone had a favorable effect, as evidenced by more rapid disappearance of edema, early drying of the rash and a minimum of scarring. No fresh vesicles appeared once treatment was established, and pain was less during the course of the illness. They also believed that the earlier prednisone was begun, the better the result, but that it was necessary to continue treatment after the early improvement. The steroid therapy seemed to have no effect on the incidence of postherpetic neuralgia or of ophthalmic complications, but they thought that there was a beneficial effect on these complications when they occurred.

Carter and Royds also considered the use of antibiotics to be essential, for without them septicemia might well be a complication of the secondary skin infections. Interestingly enough, the senior author,[4] in a controlled study, had previously shown that antibiotics have no demonstrably favorable effect on the course of herpes zoster, and this was corroborated by Kass *et al.*[5]

Carter and Royds[3] also reviewed the results reported by several other groups and concluded that it appears established that ocular complications of herpes zoster respond to local and systemic administration of corticosteroid drugs, but that there is nothing to suggest that these drugs influence the incidence of the complications. Another review of experience with various forms of treatment in a large number of cases, including 11 patients treated with adrenocorticosteroids, was reported at about the same time by Epstein and Allington[6] before a group of dermatologists. These authors concluded that, by their criteria, every type of treatment used failed to shorten the course of the disease. After the presentation of these findings, several discussors agreed, but others expressed their impression that the combination of cyanocobolamin with prednisone was highly beneficial in herpes zoster, even including the late neuralgias.

During the past few months several physicians, in letters to the editor of the *British Medical Journal*, have mentioned cases of herpes zoster occurring during ACTH or adrenocorticosteroid therapy of other diseases. Creighton and Dewar[7] reported a case in which ACTH did not suppress the onset or ameliorate the progress of herpes zoster occurring during maintenance therapy of mycosis fungoides. They also cited a report by McNichol in which the Ramsay-Hunt syndrome developed in a patient under treatment with cortisone for ulcerative colitis.

Breen,[8] commenting on this report, noted that he had used cortisone in a small number of cases of herpes zoster in which the reaction appeared to be excessive, with high fever, bleeding or gross edema of the eyelids, and thought that he obtained good results although he could not claim that they were outstanding. He noted, however, that generalized, attenuated chicken-pox eruption followed the use of this treatment more often than he had seen in his earlier experience.

O'Driscoll,[9] commenting in turn on Breen's letter, reported his own experience "lest somebody be tempted to use steroids in herpes zoster." He observed a patient in whom herpes zoster developed during treatment with prednisolone for rheumatic fever. In his patient, the zoster lesions took two months to heal, and the "scar was most unsightly."

Thus, herpes zoster provides another example of favorable results from adrenocorticosteroid therapy enthusiastically reported in uncontrolled cases or groups of cases, whereas in similar cases the results reported by others are obviously unfavorable or the drugs are without effect, and still others report the development of the same infection during treatment of other conditions with these hormones.

In this connection, it is well to recall the report of Haggerty and Eley[10] on 12 fatal cases among children who were receiving cortisone for other diseases at the time when they contracted varicella, and the occurrence of 2 cases of unusually severe herpes zoster in children who were receiving hormone therapy.[11] Evidence for the identity of the causative viruses of varicella and herpes zoster has been presented recently by Weller and his co-workers.[12, 13]

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8. Cortisone and Herpes Zoster. Correspondence. New England J. Med., *261:* 1033–1034, 1959.

To the Editor: The editorial, "Cortisone and Herpes Zoster," in the September 3 issue of the *Journal* concludes, "Thus, herpes zoster provides another example of favorable results from adrenocorticosteroid therapy enthusiastically reported in uncontrolled cases or groups of cases, whereas in similar cases the results reported by others are obviously unfavorable or the drugs are without effect. . . ."

Apparently, this conclusion is based largely on the 3 cases occurring during steroid therapy cited by Creighton and Dewar, McNichol and O'Driscoll, as well as Breen's comment that "generalized, attenuated chicken-pox eruption followed the use of (steroid) treatment more often than he had seen in his earlier experience."

In addition, the editorial sounds the ominous knell that more fatalities can be expected in patients with herpes zoster treated with steroids. As evidence, it quotes the report of Haggerty and Eley on 12 fatal cases "among children who were receiving cortisone for other diseases at the time when they contracted varicella, and the occurrence of 2 cases of unusually severe herpes zoster in children who were receiving hormone therapy." Furthermore, it notes that "evidence for the identity of the causative viruses of varicella and herpes zoster has been presented recently by Weller and his co-workers."

In favor of steroid treatment, the editorial cites 15 cases by Carter and Royds with "favorable effect . . . [but] no effect on the incidence of postherpetic neuralgia or of ophthalmic complications, but . . . a beneficial effect on these complications when they occurred." It grants that the favorable effects were probably not from the coincident antibiotics used, but from the steroids.

As further evidence favoring the use of steroids, I call attention to 11 additional cases reported by Scheie and Alper in an article entitled "Treatment of Herpes Zoster with Cortisone or Corticotropin" (A.M.A. Arch. Ophth., *53:* 38–44, 1955), in which 15 successfully treated cases (11 not cited in the *Journal's* analysis) in the literature are reviewed. Their own additional 11 cases were treated with steroids for 3 to 90 days, with relief of pain, "striking improvement . . . in the ocular lesions," and most of the visual

results returning to 6/6 level. The secondary glaucoma and uveitis generally cleared promptly, thereby reducing the long-term threat to vision. The corneal scarring was markedly diminished after the inflammatory edema left the tissue. They concluded that this therapy was merely suppressive, not curative.

I believe that these 11 cases, in addition to the 11 reported in the review, as well as the 15 successful cases of Carter and Royds, present sufficient reason for the cautious continued treatment with steroids for stubborn cases of herpes zoster ophthalmicus. The editorial, although perhaps intended only for an admonition, sounded like a condemnation of such therapy. Evidence presented for such a condemnation was too scanty for removal of such therapy from our armamentarium.

JOSEPH AMDUR, M.D.
Long Beach, Long Island, New York

Note: In the editorial in question there was no granting that the favorable effects were attributable to steroids any more than to antibiotics. Since groups of cases that were adequately controlled and strictly comparable by random selection have not been reported, no cause-and-effect relation can be inferred. Any unnecessary and unproved therapy may be condemned if it has potentials for harm, and it is still maintained that the value of steroids in the treatment of herpes zoster has not been demonstrated.—ED.

9. Corticosteroids in Ophthalmology. Correspondence. Brit. M. J., Jan., 60–61, 1960.

SIR,—Your annotation (*Journal*, November 21, p. 1079) on corticosteroids in ophthalmology deserves some comment. While agreeing wholeheartedly about the great benefits when applied to suitable conditions, and the even greater dangers attached to their indiscriminate use, the greatest danger is surely the self-deception of thinking that the combination with an antibiotic makes their use safe. The combination is mentioned, though indirectly, for infective corneal ulceration, but I hope it was not meant as a recommendation. I can't imagine that the antibiotic will still be effective when the local defences are hindered by the cortisone. It is likely to turn a relatively simple condition into a chronic one, and at the same time to encourage drug-resistant organisms. In cases of infective corneal ulcer, cortisone (and the other corticosteroids) is certainly not wanted while the infective organisms are present, and after these have been eradicated (by the body's defences aided, if you like, by unadulterated antibiotics) there is seldom any need for cortisone.

With plain antibiotic used frequently, either an infection clears up quickly or one realizes within a couple of days that the organism (virus or bacterial) is resistant. If cortisone also is given, the inflammatory reaction (which after all is most of the signs and symptoms and the local defence mechanism) is damped down and the eye appears to be improving, when actually the infection is probably spreading more deeply. The practically white chronic keratitis described by Mr. Abrams (*Journal*, April 25, p. 1116) is becoming all too common nowadays and results in far more permanent scarring than a short-lived acute ulcer. In iritis, rosacea keratitis, and allergic conditions, cortisone works wonders indeed, but antibiotics are quite unnecessary.

These combinations are a form of blunderbuss therapy which has little to recommend it. In cases of cure one does not know which drug was effective, and one spoils the chance of learning from one's cases. In cases of failure one may have neutralized one drug by the other. Their use is as sensible as treating with a combination of eserine and atropine an eye one suspects of having either iritis or glaucoma; one cannot decide which, but hopes thereby to cope with both. There may be a case for the occasional use of these combinations, but it is certainly not in the ordinary run of sore eyes.—I am, etc.,

J. PRIMROSE
Oldchurch Hospital, Romford, Essex

10. Corticosteroids in Ophthalmology. Correspondence. Brit. M. J., Feb., 501–502, 1960.

SIR,—During the past few months I have had under my care 3 cases of moderately severe hypopyon ulcer of the cornea. These were treated, in the first place, by the usual orthodox methods including carbolization, atropine, and antibiotics by instillation, subconjunctival penicillin and streptomycin, artificial pyrexia, and sulphonamides by mouth. The first case did not respond to these methods, and, after some hesitation and rather in desperation, drops containing neomycin and hydrocortisone were instilled at frequent intervals. There was a dramatic improvement and clearing of the hypopyon followed by relapse when these drops were stopped. Further treatment with them resulted in cure of the hypopyon ulcer with a minimum of scarring.

In the other two cases orthodox methods were again tried, without a good response and the same antibiotic and hydrocortisone drops were then given with the same prompt improvement and eventual cure. As antibiotic drops and subconjunctival injections had already been given without any marked improvement, I think it is reasonable to conclude that the addition of the hydrocortisone was a most vital factor in bringing about the immediate improvement, and I myself have no doubt that these hypopyon ulcers were cured largely because of, and not in spite of, the addition of hydrocortisone to the treatment. And why should not that be so? Surely a substance which will reduce inflammatory oedema and exudation, and venous stasis, will have a beneficial effect by allowing the defences of the body and the antibiotics to get to the inflamed parts more easily.

These cases make me wonder whether Mr. J. Primrose (*Journal*, January 2, p. 60), who condemns so vigorously the use of these combinations of an antibiotic and hydrocortisone, has ever used them. He doesn't say that he has, and his entire condemnation is based on vague theoretical grounds. In that case, why should he refer so scathingly to these combinations of only two substances (with complementary actions) as blunderbuss therapy? And, regarding his comparing their use to giving a mixture of atropine and eserine (with antagonistic actions), this seems to be a ridiculous analogy. The corticosteroids either alone or in combination with an antibiotic are not given because a diagnosis is in doubt (as Mr. Primrose suggests) but because there isn't other treatment as effective. And, contrary to what you state in your annotation on this subject (*Journal*, November 21, p. 1079), in my experience the corticosteroids are most beneficial in some virus diseases of the eye—*e.g.*, the keratitis and iritis of herpes zoster ophthalmicus—and in many cases of chronic corneal disease, if they don't cure, they often give most marked symptomatic relief, quite unobtainable by other means, which certainly the patients welcome.

Ophthalmologists are fortunate in being able to see what is happening to the inflamed eye and can regulate their treatment accordingly, and if by chance they think hydrocortisone is being harmful, or not helpful, they can stop it without dire consequences. In my opinion there is a tendency at the present time to exaggerate possible dangers in its local use in the eye.—I am, etc.,

A. C. SHUTTLEWORTH
Chester

IMPRESSIONS GATHERED FROM A REVIEW OF THE LITERATURE ON HERPES ZOSTER AND CORTICOSTEROID OR ACTH THERAPY

1. If steroids or ACTH are given *after* the herpes zoster has developed there is relief of pain but no consistent or appreciable effect on the basic course of the disease. The therapy seems to have an anti-inflammatory effect.

2. If a patient develops herpes zoster at a time when he is *getting* steroids or ACTH he

may have a prolonged, complicated course with necrosis or gangrene of the skin areas and generalized spread of the skin lesions over the body.

Thus it appears that if a subject (not getting steroid or ACTH therapy) develops herpes zoster, antibody formation is usually promptly and satisfactorily stimulated and subsequent therapy with steroids does not alter the healing phase of the disease. The therapy exerts its nonspecific antiphlogistic effect.

On the other hand if a herpes zoster infection develops while a patient is getting a significant amount of steroids, satisfactory antibody formation *may be* interfered with and lead to a complicated course.

It also appears that ACTH therapy or corticosteroid therapy can stimulate the chicken pox virus into a more virulent organism and apparently allow the development of herpes zoster as a complication. There is a close relationship between these two viruses if they are indeed not one virus.

LEONARD APT AND IRVING H. LEOPOLD

Classics of Ophthalmology
JAMES E. LEBENSOHN, *Editor*

MAGNIFYING-GLASSES

FRIAR ROGER BACON

Oxford, England

Excerpt from Opus Majus, 1267

(From the translation by J. H. Bridge, M.D., The Opus Majus of Roger Bacon, Oxford, 1897.)

If anyone examines letters or other minute objects through the medium of crystal or glass or other transparent substance, if it be shaped like the lesser segment of a sphere, with the convex side towards the eye, and the eye being in the air, he will see the letters far better, and they will seem larger to him. For according to our canon concerning a spherical medium beneath which the object is placed, the centre being beyond the object, the convexity being towards the eye, all causes agree to increase the size, for the angle in which it is seen is greater, the image is greater, and the position of the image is nearer, because the object is between the eye and the centre. For this reason such an instrument is useful to old persons and to those with weak eyes, for they can see any letter, however small, if magnified enough. But if a larger segment of a sphere be employed, then, according to our canon the size of the angle is increased, and also the size of the image, but propinquity is lost because the position of the image is beyond the object, the reason being that the centre of the sphere is between the eye and the object seen. Therefore such an instrument is not of so much use as the smaller portion of a sphere.

Objects are greater when the vision is refracted; for it easily appears by the above-mentioned canons that very large objects may seem to be very small and conversely, and those at a great distance away may seem very near and conversely. For we can so form glasses and so arrange them with regard to our sight and to objects that the rays are refracted and deflected to any place we wish, so that we see the object near at hand or far away beneath whatever angle we desire. And so we can read the smallest letters or count grains of sand or dust from an incredible distance owing to the magnitude of the angle beneath which we see them, and again the largest objects close at hand might be scarcely visible owing to the smallness of the angle beneath which we view them; for it is on the size of the

ROGER BACON. Born near Ilchester, about 1214; died probably at Oxford in 1292.

angle on which this kind of vision depends, and it is independent of distance save per accidens. So a boy can appear a giant, a man seem a mountain, and in any size of angle whatever, for we can see a man under as large an angle as though he were a mountain and make him appear as near as we desire. So a small army might seem very large, and though far away appear near, and conversely: so, too we could make sun, moon, and stars apparently descend here below, and similarly appear above the heads of our enemies, and many other similar marvels could be brought to pass, that the ignorant mortal mind could not endure the truth.

As to double refraction, what is causally manifest with regard to it we can verify in many ways by the results of experiment. For if anyone holds a crystal ball or a round urinal flask filled with water in the strong rays of the sun,

standing by a window in face of the rays, he will find a point in the air between himself and the flask at which point, if any easily combustible substance is placed, it will catch fire and burn, which would be impossible unless we suppose a double refraction. For a ray of the sun coming from a point in the sun through the centre of the flask is not refracted, because it falls perpendicularly on flask, water, and air passing through the centre of each. . . . But all the other rays given forth at the same point in the sun from which this perpendicular ray comes are necessarily refracted in the body of the flask, because they fall at oblique angles, and since the flask is denser than air, the refraction passes between the straight path and the perpendicular drawn from the point of refraction to the centre of the flask. And when it passes out again into the air, then, since it comes upon a less dense body, the straight path passes between the refraction and the perpendicular drawn from the point of refraction, so that the refracted ray may fall upon the first perpendicular which comes without refraction from the sun. Now since an infinite number of rays are given off from the same point of the sun, and one only falls perpendicularly on the flask, all the others are refracted and meet at one point on the perpendicular ray which is given off along with them from the sun, and this point is the point of combustion. On it are collected an infinite number of rays, and the concentration of light causes combustion. But this concentration would not take place except by double refraction, as shown in the diagram.

Editorial Comment: The beginnings of spectacles is veiled in medieval mystery. They first appeared toward the end of the 15th century in both Europe and China, but the differences between the earliest spectacles of West and East suggest a possible independent development. In ancient Greece and Rome lenses were used only as "burning glasses." The Opus Majus of Roger Bacon contains the first mention of the employment of lenses as a means of assisting sight. The Friar's knowledge may have been inspired by the writings of Alhazen or derived from eastern missionaries; in turn, the transfer of Bacon's ideas to Italy by a member of his order would account for the introduction of spectacles there, first by Salvino d' Armati and subsequently by Alessandro di Spina.

At first the use of glasses was opposed by both priest and physician. The clergy regarded the device as an impertinent effort to defeat the divine purpose of inflicting disabilities on the aged; and the physicians, fearing that the eyes were thereby eventually weakened, regarded the prescribing of glasses as beneath their dignity. By the 15th century spectacles had attained social approbation and it became customary to picture with spectacles characters of dignity and importance. In 1480 Ghirlandajo painted Saint Jerome at a desk from which dangled a pair of nose-glasses. This detail inspired the legend that the learned saint was the inventor of spectacles and so Saint Jerome became the patron of the spectacle makers' guild.

Lenses were orginally used for the relief of presbyopia and "for old sight in young people." A myopic correction is first pictured in the portrait of Pope Leo X, painted by Raphael in 1517, which now hangs in the Palazzo Pitti of Florence. In 1628 Daca de Valdes of Seville published the first discussion of refraction in a quarto of 100 pages in which cataract lenses are mentioned.

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Biographical Note

Roger Bacon (1214–1294) was born in England of a noble family. He studied at Oxford and then at Paris for the degree of Doctor of Theology, mastering at the same time physics, mathematics, Latin, Greek, Hebrew and Arabic. At the age of 36 he returned to London, joined the Franciscan monks, and became an instructor at Oxford. His scientific experiments were looked upon with suspicion. After a few years his lectures were interdicted and he spent the next 10 years in a Paris prison in solitary confinement, until the accession of Pope Clement IV. The world owes a great debt to this dignitary, a man of liberal culture, who requested from Bacon to whom he was friendly some treatises on science. In 18 months Bacon completed three immense volumes, the Opus Majus, the Opus Minus, and the Opus Tertium—works which inspired a new era in the world of physical science. With the advent of the next pope 3 years later Bacon was thrown again into prison and all his books were condemned. This second confinement lasted 14 years, just 2 years before his death at the age of 80. For centuries this martyr of science was regarded as a wizard. "The Famous Historie of Fryer Bacon" related how by the wave of a magic wand he summoned excellent music such as had never been heard before; and by another wave of the wand brought tables covered with the richest fruit, and so on.

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Book Review

The Story of Contact Lenses, by PHILIP L. SALVATORI. Obrig Laboratories Inc., Library of Congress Catalog Card No. 60–12195. $3.75. Obrig Laboratories Inc., Box 791, Sarasota, Florida.

This book is a beautifully produced and informative one on contact lenses published by Obrig Laboratories, Inc. It represents a nontechnical presentation of the subject. Dr. Salvatori is an author of standard professional textbooks on contact lenses and he conducts contact lens seminars around the country for those engaged in fitting contact lenses. The present volume was written with the lay reader as well as the professional in mind. It would seem to have its greatest purpose for use in the waiting room for the perusal of patients who are contemplating the use of contact lenses and want some authoritative information concerning them.

The book is divided into several sections; the first explains the fascinating history of the development of contact lenses since the early 19th century, how the present lenses work and how they are made. The final section is headed "a word of caution" and stresses that only specialists in the field of eye care are qualified to decide who should use contact lenses and which lenses are best suited for a particular patient.

The book contains many fine photographs, woodcuts and drawings. It really represents a work of art, as there are handmade papers which set off each colorful section. The entire book includes only 58 pages bound in a hard cover of black linen.

IRVING H. LEOPOLD

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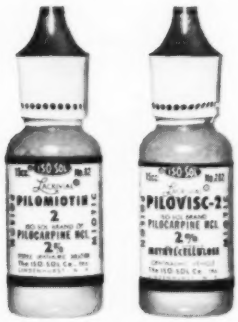

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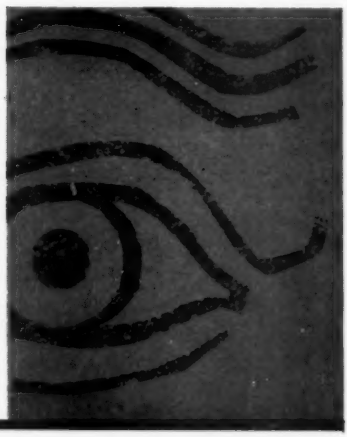

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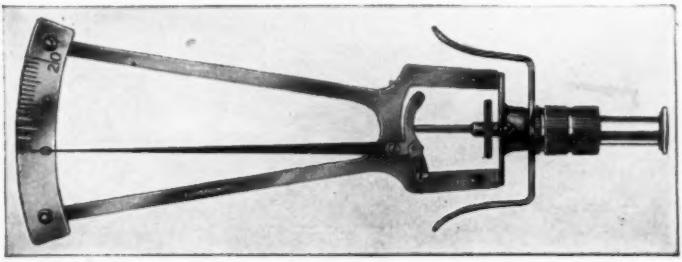

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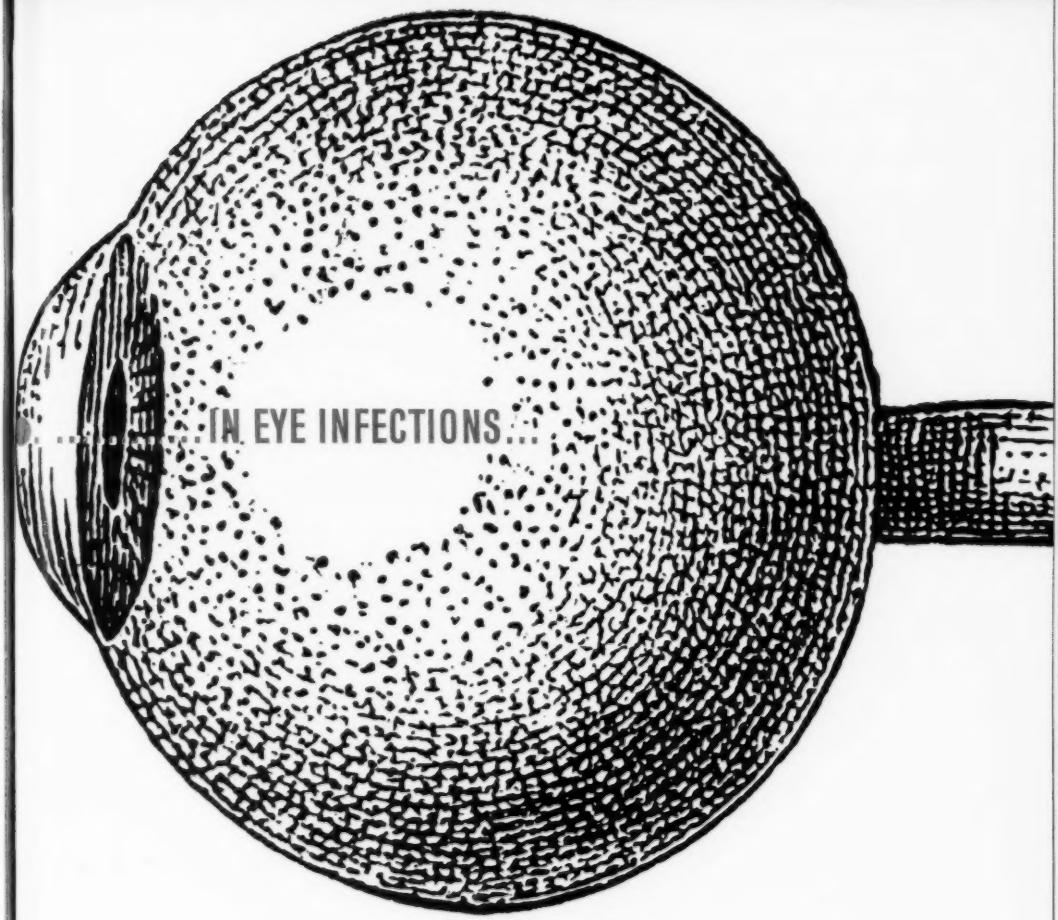

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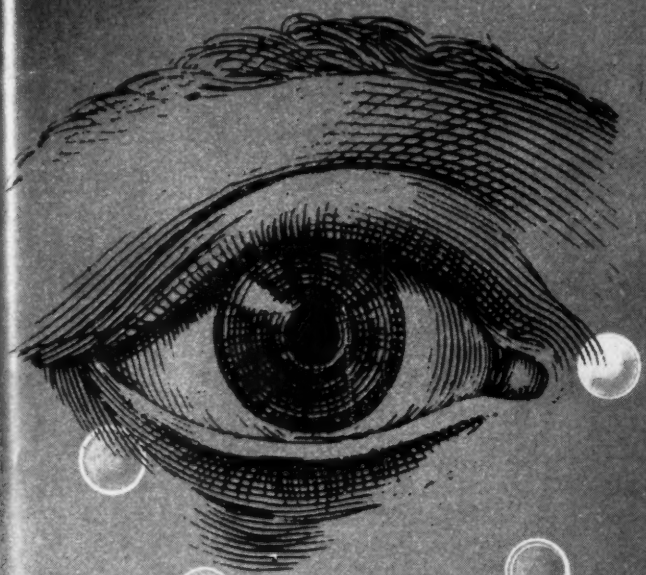

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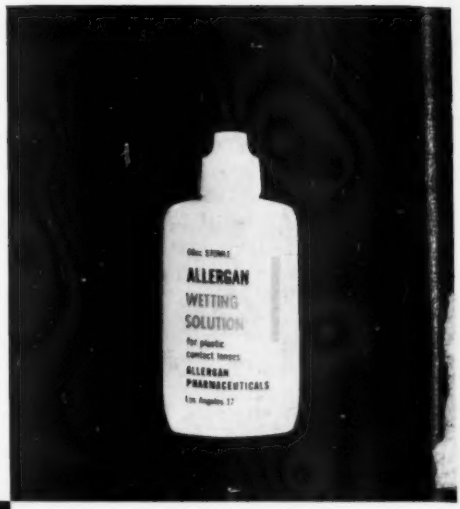

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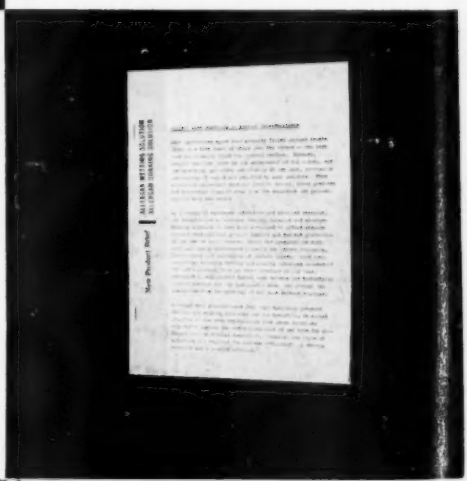

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